Rapid Evidence Review

Tocilizumab in the management of COVID-19.

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National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

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Key changes (highlighted in yellow) (highlighted in yellow) between 5 (23rd of October 2020) and version 6 (17th of February 2021): Updated evidence relating to tocilizumab in COVID-19 added. Only RCTs with patients treated with tocilizumab in COVID-19 (n=3) have been included in the evidence review update.

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Extrapolation of evidence from cytokine-driven hyperinflammatory-related disorders intimates that patients who have severe COVID-19 with hyperinflammation could benefit from tocilizumab. Eight RCTs have reported the results of tocilizumab versus placebo plus standard of care (SOC) in patients with COVID-19. Earlier RCTS (n=6) have reported mixed results suggesting no clear benefit associated with tocilizumab monotherapy on survival outcomes or other important endpoints including duration of hospital stay, need for invasive mechanical ventilation, disease progression and time to recovery in patients with COVID-19. However, the majority of patients included in these trials did not routinely receive corticosteroids as part of SOC, were earlier in their disease course, were not critically unwell or did not display evidence of an inflammatory phenotype (1–6). There is evidence that tocilizumab in combination with systemic corticosteroids and SOC improves mortality and other important endpoints in critically ill patients with COVID-19 receiving organ support in intensive care. The benefit is also observed in a subset of hospitalised patients with severe COVID-19 who demonstrate evidence of progressive COVID-19 characterised by an inflammatory phenotype (CRP ≥75 mg/L) and hypoxaemia (oxygen saturation <92% on air or requiring oxygen therapy) outside of the ICU setting (7,8). The differing efficacy results between earlier RCTs and more recent (REMAP-CAP and RECOVERY) RCTs appear to be driven by the concomitant administration of tocilizumab in combination with systemic corticosteroids and strict patient selection rather than the timing of administration of tocilizumab from onset of symptoms or the setting of administration.

Summary of individual RCTs

BACC Bay Tocilizumab Trial recruited moderately ill hospitalized patients (n=243) with Covid-19 with an enrolment requirement of two of fever (>38^{o}C), pulmonary infiltrate or need for supplemental oxygen and laboratory defined evidence of a hyperinflammatory state (either CRP>50mg/L, ferritin >500ng/ml, d-dimer>1000ng/ml or LDH > 250u/L). No patients were receiving mechanical ventilation, 80% of patients were receiving supplemental oxygen, 4% were receiving high flow oxygen and 16% were not receiving supplemental oxygen at baseline. Tocilizumab was not effective for preventing intubation or death in this moderately ill hospitalized cohort with Covid-19 (HR for intubation or death: 0.83 (95%CI 0.38-1.81 p=0.64). While no patients received concomitant dexamethasone,11% in the tocilizumab arm and 6% in the placebo arm received other glucocorticosteroids (3).

CORIMUNO-TOCI-1 recruited patients (n=130) with moderate to severe COVID-19 pneumonia requiring oxygen support (≥3 L/min) who did not require ventilation or admission to the intensive care unit (ICU) at baseline. Glucocorticoids were administered to 33% of patients in the tocilizumab arm and 61% in the placebo arm. Tocilizumab did not reduce the risk of disease progression as there was no observed reduced risk of a WHO-CPS score of greater than 5 at day 4. The proportion of patients with non-invasive ventilation, intubation, or death at day 14 was 36% with usual care and 24% with tocilizumab (median posterior HR: 0.58; 90% credible intervals [CrI], 0.33 to 1.00). No difference in mortality at 28 days was found between the two arms (2).

RCT-TCZ-COVID-19 (n=126) assessed the efficacy of early administration of tocilizumab in patients with COVID-19 with mild acute respiratory failure (PaO_2/FiO_2 ratio between 200 and 300 mm/Hg), and an inflammatory phenotype defined by a fever or elevated CRP levels (≥ 10 mg/dL and/or CRP level increased to at least twice the admission measurement). Patients were allowed oxygen therapy at baseline but not mechanical ventilation. In total 10% of patients in the tocilizumab arm and 14% in the SOC arm received corticosteroids. No benefit on disease progression was observed compared with

SOC (clinical worsening within 14 days since randomization rate ratio [RR]: 1.05; 95% CI, 0.59 to 1.86, p=0.87) and no difference on day 14 or day 30 mortality was found (9).

EMPACTA trial enrolled patients (n=389) with COVID-19 who were not receiving invasive or non-invasive mechanical ventilation at baseline and were at an earlier disease stage. In total, 80.3% in the tocilizumab arm and 87.5% in the placebo arm received systemic glucocorticoids. The primary outcome was a composite of mortality or invasive mechanical ventilation at Day 28, which favoured tocilizumab over placebo (12.0% in the tocilizumab arm vs. 19.3% in the placebo arm; HR 0.56; 95% CI, 0.33 to 0.97; p= 0.04). However, there was no difference between the treatment arms in all-cause mortality at Day 28 (6).

COVACTA included patients (n=452) with severe COVID-19 disease. There was no difference between the arms in the primary outcome, clinical status (based on a seven-point ordinal scale) at Day 28 (OR 1.19; 95% CI, 0.81 to 1.76), or overall mortality. Glucocorticoid use was higher in the placebo arm both at baseline and during the trial (28.5% and 52.1%) 33.7%), than in the tocilizumab arm (19.4% and 33.7%) (5).

Veiga *et al* 2021 included patients (n=129) with *severe or critical COVID-19* who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (D dimer >2.74 nmol/L, CRP >50 mg/L, ferritin >300 µg/L, or lactate dehydrogenase greater than the upper limit of normal). In total 84% in the tocilizumab arm and 89% in the SOC arms received concomitant corticosteroids. Adding tocilizumab to SOC when compared with SOC alone did not reduce the risk of mechanical ventilation or death at 15 days (28 versus 20 percent, OR 1.54, 95% 0.7-3.7), and there was a trend toward higher 28-day mortality with tocilizumab (21 versus 9 percent, OR 2.7, 95% CI 0.97-8.35) (4)

REMAP-CAP included critically ill patients admitted to ICU who were receiving organ support (respiratory or cardiac). At baseline 28.8% required high-flow oxygen, 41.5% required non-invasive mechanical ventilation, and 29.4% required invasive mechanical ventilation. Tocilizumab decreased in-hospital 28-day mortality (28% tocilizumab vs. 36% SOC died), improved in-hospital survival (adjusted odds ratio [OR]: 1.64; 95% CrI, 1.14 to 2.35), and increased the number of organ support-free days (adjusted OR: 1.64; 95% CrI, 1.25 to 2.14). Over 80% of patients across both arms received concomitant systemic corticosteroids (8).

RECOVERY recruited patients with severe COVID-19 who displayed evidence of progressive disease with evidence of both hypoxia (SpO_2 <92% on room air or requiring O_2 therapy) and evidence of systemic inflammation (CRP ≥75 mg/L). At randomisation, 14% of patients were receiving invasive mechanical ventilation, 41% were receiving non-invasive respiratory support (including high-flow nasal oxygen, continuous positive airway pressure, and non-invasive ventilation), and 45% were receiving no respiratory support other than simple oxygen therapy. The primary outcome was 28-day mortality. Tocilizumab in combination with usual care (including corticosteroids) was shown to reduce the relative risk of death from COVID-19 at day 28 by 14% relative to usual care (RR: 0·86; 95% CI 0·77 to 0·96; p=0·007) and the absolute risk of mortality by 4%; 596 (29%) of the 2022 patients randomised to tocilizumab and 694 (33%) of the 2,094 patients allocated to usual care died within 28 days (7). In a subset of hospitalised patients with severe COVID-19 the effect size of tocilizumab when combined with systemic corticosteroids (28-day mortality RR =0.80, 95% CI 0.70 to 0.90) is larger than that reported in the overall study results (28-day mortality RR: 0.86, 95% CI 0.77 to 0.96, p=0.007) which included patients who did not receive systemic corticosteroid therapy (n=357/2022 (18%) in the tocilizumab arm, n=367/2094 (18%) in the SOC arm). The mortality benefit was not seen in patients receiving tocilizumab monotherapy (RR: 1.16, 95% CI 0.91- 1.48) (7).

Conclusion

There is no clear evidence that tocilizumab monotherapy has a benefit on disease progression or survival outcomes in patients with COVID-19 (1–6). Tocilizumab in combination with systemic corticosteroids and SOC may reduce mortality and also avoid progression to invasive mechanical ventilation in a subset of hospitalised patients with severe COVID-19 characterised by an inflammatory phenotype (CRP ≥75 mg/L) and hypoxaemia (oxygen saturation <92% on air or requiring oxygen therapy). It is unclear if hypoxic patients with severe COVID-19 and a CRP <75mg/L would benefit from tocilizumab in combination with systemic corticosteroids (7). The administration of tocilizumab in combination with systemic corticosteroids is likely to offer mortality benefit in critically ill patients within 24 hours of ICU admission. No change in frequency of known or unknown adverse events have been observed in the tocilizumab arm over standard of care (8).

Introduction

Although the mechanisms of COVID-19–induced lung injury are still being elucidated, the prevailing theory is that an excessive immune response induced by cytokine storm manifested by elevated IL-6 and other pro-inflammatory cytokines are key drivers of both lung damage and mortality in COVID-19 (10,11). It is unclear whether IL-6 represents a biomarker or a central pathogenetic element of severe COVID-19 that should be used as a parameter for therapeutic intervention. There is also a growing recognition of the uncertainty surrounding the role of IL-6 in CRS driven severe COVID-19.

Tocilizumab is a humanised anti-IL-6 antibody licensed for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and giant cell arteritis. It is also licensed for the induction of the rapid reversal of cytokine release syndrome (CRS), a form of cytokine storm caused by CAR-T treatment (12). Interleukin-6 (IL-6) is a key pro-inflammatory cytokine that is elevated in CRS. Suppression of proinflammatory interleukin-1 (IL-1) family members and IL-6 are likely to have a therapeutic effect in many inflammatory diseases, including viral infections (13). It has been suggested that the inhibition of IL-6 may help attenuate the CRS in severely ill patients with COVID-19 by reducing cytokine concentrations and acute phase reactant production (14,15). Tocilizumab prevents IL-6 from binding to soluble and cell associated IL-6 receptors inhibiting IL-6-mediated signalling (16).

In early December 2019 a novel enveloped RNA betacoronavirus was recognised as the cause of pneumonia cases of unknown origin. The virus is phylogenetically similar to SARS-CoV and has been designated SARS-CoV-2. Emerging studies highlight the characteristics of COVID-19 infected patients (17–19). Clinical data suggests that disease progression in COVID-19 infected patients may be driven by a dysregulated immune response resulting in a cytokine storm (20). Cytokine release syndrome (CRS) is a diverse set of conditions associated with the clinical phenotype of systemic inflammation, multi-organ failure, hyperferritinaemia and high mortality (21). The condition is associated with inflammation in a dysregulated positive feedback loop with elaboration of inflammatory cytokines including IL-6. In CAR-T cell-associated CRS, IL-6 is thought to be a key driver of symptoms (22). Several studies including two meta-analyses have suggested that IL-6 levels are significantly elevated in patients with COVID-19 and are associated with adverse clinical outcomes suggesting that IL-6 could potentially serve as an effective biomarker for predicting disease progression in patients with COVID-19 (23–29). Tocilizumab has shown efficacy for other iatrogenic causes of CRS and has demonstrated rapid improvements, typically within 48 hours of administration, in patients with CRS treated with CAR-T cells, for which it is licensed (22,30,31). Observational studies to date have suggested that tocilizumab may be an effective therapeutic strategy to counteract or dampen the intensity of the cytokine storm that may develop in conjunction with virally-induced ARDS in COVID-19 (20).

Critical appraisal of studies reporting the use of tocilizumab in COVID-19

A rapid critical appraisal of the phase III trial study results and the phase II trial results which included patients treated with tocilizumab in COVID-19 was conducted by the ERG. The search strategy is outlined in Appendix 1.

Randomised controlled trials

Boston Area COVID-19 Consortium (BACC) Bay

Stone *et al* reported the results of the Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial; a randomized, double-blind, placebo-controlled study to evaluate the effects of tocilizumab compared to placebo on patient outcomes in participants (n=243) moderately ill with confirmed SARS-CoV-2

infection and evidence of systemic inflammation. Patients had to have at least two of the following signs: fever (body temperature >38°C) within 72 hours before enrolment, pulmonary infiltrates, or a need for supplemental oxygen in order to maintain an oxygen saturation higher than 92%. At least one of the following laboratory criteria also had to be fulfilled: a CRP level higher than 50 mg/L, a ferritin level higher than 500 ng per millilitre, a d-dimer level higher than 1000 ng per millilitre, or a lactate dehydrogenase level higher than 250 U/ L. A total of 194 patients (80%) were hospitalized in non-ICU hospital wards and were receiving supplemental oxygen (≤6 litres per minute), delivered by nasal cannula, to maintain an oxygen saturation greater than 92%; 10 (4%) were receiving high flow oxygen (>6 and ≤10 litres per minute delivered by any device); and 38 (16%) were not receiving supplemental oxygen at baseline. The hypothesis underlying the trial was that IL-6 receptor blockade in patients with disease that had not yet led to intubation would disrupt the cytokine storm associated with COVID-19, could limit progression of hypoxemic respiratory failure necessitating intensive care, mechanical ventilation and improve mortality. Patients were randomly assigned in a 2:1 ratio to receive SOC plus a single dose of either tocilizumab (8 mg/kg) (n=161) or placebo (n=81). Median CRP was 116 (IQR: 67.1 – 190.6) mg/L in the tocilizumab arm and 94.3 (IQR: 58.4 – 142.0) mg/L in the placebo arm. A total of 194 patients (80%) were hospitalized in non-ICU hospital wards and were receiving supplemental oxygen (≤6 litres per minute), delivered by nasal cannula, to maintain an oxygen saturation greater than 92%; 10 (4%) were receiving high flow oxygen (>6 and ≤10 litres per minute delivered by any device); and 38 (16%) were not receiving supplemental oxygen at baseline.

The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses.

Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 with evidence of hyperinflammation. The hazard ratio (HR) for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% CI 0.38 to 1.81). A comparable proportion of participants in the tocilizumab and placebo arms experienced the primary endpoint of intubation or death over 28 days of follow-up, with rates of 10.6% and 12.5%, respectively. Rates of clinical worsening on an ordinal scale were also similar in the two groups, at a corresponding 19.3% and 17.4%. Of note, patients in the tocilizumab arm (n=18) and the control arm (n=5) received other concomitant agents including remdesevir and glucocorticoids. No patients received concomitant dexamethasone as the BACC Bay trial preceded the publication of the RECOVERY trial regarding the efficacy of dexamethasone in COVID-19. However, other concomitant glucocorticoids were permitted. Glucocorticoids (unspecified) were administered to 23 patients (n=18 [11%] in the tocilizumab group and n=5 [6%] in the placebo group. The authors reported that the findings from their study did not provide support for the concept that early IL-6 receptor blockade was an effective treatment strategy in moderately ill patients hospitalized with COVID-19. Stone *et al* concluded that tocilizumab had no significant effect on the risk of intubation or death, on disease worsening, on time to discontinuation of supplemental oxygen, or on any of the efficacy outcomes examined. However, the investigators highlighted that they could not exclude the possibility that tocilizumab treatment was associated with either some benefit or harm in some patients because of the width of the confidence intervals for the efficacy comparisons (3).

CORIMUNO-TOCI-1

CORIMUNO-TOCI-1 was a multicentre, open-label, randomized, controlled trial which evaluated tocilizumab for the treatment of *moderate or severe COVID-19* associated pneumonia across 9 treatment centres in France. Key inclusion criteria were a diagnosis of COVID-19 pneumonia confirmed

by positive PCR and/ or by CT scan, with moderate or severe COVID-19 pneumonia requiring at least 3 L/min of oxygen but without ventilation or admission to the intensive care unit upon admission to hospital. Patients recruited to the study were randomly assigned to receive tocilizumab (8 mg/kg), intravenously plus SOC on day 1 and on day 3 if clinically indicated or to receive SOC alone. SOC was defined as antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants which was provided at the discretion of the treating physicians. The primary outcomes assessed in the study were the proportion of patients dead or needing non-invasive or mechanical ventilation on day 4 (defined as scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS)); and survival with no need for non-invasive or mechanical ventilation at day 14. The day 4 and 14 outcomes were amended on April 6, 2020, to include high-flow oxygen in non-invasive ventilation to be consistent with the WHO-CPS definition. Prespecified secondary outcomes were clinical status assessed with the WHO-CPS scores at day 7 and day 14, overall survival, time to discharge, time to oxygen supply independency, biological factors such as C-reactive protein level, and adverse events. All analyses were performed on an intention-to-treat basis however no adjustment for multiplicity was considered for secondary outcomes. Therefore, all analyses of the secondary endpoints should be considered exploratory and are not considered further in this review. Of 131 patients, 64 patients were randomly assigned to the tocilizumab arm and 67 to SOC arm; one patient in the tocilizumab arm withdrew consent and was not included in the analysis, and three patients did not receive tocilizumab due to death (n = 1), technical problems (n = 1), and patient refusal (n = 1). During the trial, antiviral drugs, glucocorticoids, and preventive or therapeutic anticoagulants were administered in 7 (11%), 21 (33%), and 59 (94%) patients, respectively, in the tocilizumab arm, and 16 (24%), 41 (61%), and 61 (91%) in the SOC arm, respectively. Additional immunomodulators were administered to one patient in the tocilizumab arm (anakinra) and four patients in the SOC group (anakinra, n = 3; eculizumab, n = 1). A subgroup analysis according to antiviral drug use at baseline was prespecified in the protocol. Analyses according to the use of corticosteroids were added post-hoc in light of the evidence published from the RECOVERY trial. The investigators used Bayesian statistical methods to assess efficacy. Treatment effect was expressed in terms of absolute risk difference (ARD) for the day 4 outcome and HR for the day 14 outcome. One of two predefined thresholds for treatment efficacy was met; the posterior probability of improved survival without the need for non-invasive or mechanical ventilation by day 14 in the treatment group was 95.05%, marginally exceeding the prespecified threshold of efficacy (greater than 95%). However, tocilizumab did not reduce the risk of disease progression as there was no observed reduced risk of a WHO-CPS score of greater than 5 at day 4. The proportion of patients with non-invasive ventilation, intubation, or death at day 14 was 36% with usual care and 24% with tocilizumab. The investigators suggested that tocilizumab may reduce the need for mechanical and non-invasive ventilation or death by day 14 but not disease progression or mortality by day 28. A key limitation of the CORIMUNO-TOCI-1 was the lack of blinding, open label study design and lack of placebo controls which may have influenced the clinical decision-making around need for subsequent therapeutic decisions including mechanical and non-invasive ventilation in the control arm. This may have impacted the results which suggested a reduced need for mechanical and non-invasive ventilation or death associated with tocilizumab. There is a second CORIMUNO study ongoing, CORIMUNO-TOCI-2, a trial conducted in patients with critical pneumonia, however results have not yet been published (2).

RCT-TCZ-COVID-19

Salvarani *et al* from the RCT-TCZ-COVID-19 Study Group (RCT-TCZ-COVID-19) reported the findings from a phase II, multicentre, open-label, randomized clinical trial aimed at assessing the efficacy of *early administration* of tocilizumab versus SOC in hospitalized patients (n=126) with COVID-19 pneumonia across 24 Italian centres. Key inclusion criteria were a diagnosis of COVID-19 pneumonia confirmed by positive PCR in a respiratory tract specimen, the presence of *mild acute respiratory failure* (PaO_2/FiO_2 ratio between 200 and 300 mm/Hg), an inflammatory phenotype defined by a

temperature greater than 38 °C during the last 2 days, and/or serum CRP ≥ 10 mg/dL and/or CRP level increased to at least twice the admission measurement. Patients were allowed to receive supplemental oxygen therapy, but not invasive or non-invasive mechanical ventilation at study enrolment but were allowed to do so post randomisation. Key exclusion criteria were ICU admission and any condition preventing future admission to ICU, such as advanced age with multiple comorbidities or patient-expressed preference not to be admitted to ICU.

The primary end point was clinical worsening within 14 days since randomization, defined by the occurrence of one of the following events, whichever occurred first i.e. admission to ICU with mechanical ventilation, death from any cause, PaO_2/FiO_2 ratio less than 150 mm Hg in one of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination. In cases of documented clinical worsening, patients could receive any therapy including steroids, while patients in the control arm were also eligible to receive tocilizumab therapy. Of note, 14 of 60 patients in the SOC arm received tocilizumab due to clinical worsening which may have impacted the study results. A protocol amendment was accepted by the ethics committee and an interim analysis for futility was conducted at one-third of the planned sample size (132 patients) due to challenges around participant enrolment due to a decrease in the incidence of COVID-19 disease in Italy. Investigators found no differences were observed in the occurrence of the primary composite end point between the tocilizumab and the control groups at 14 days (28.3% in the tocilizumab arm compared with 27.0% in the SOC arm showed clinical worsening within 14 days of randomisation (RR = 1.05, 95% CI 0.59 – 1.86, p=0.87). The investigators also reported no differences in ICU admission, discharge rates or death rates between arms, however it is noted that mortality rates at day 14 (1.7% versus 1.6%) and day 30 (3.3% vs 1.6%), and ICU admission rates at 14 days (10.0% vs 7.9%, respectively) were low in both tocilizumab and SOC arms, respectively (9). The low mortality rate is likely due to the trials exclusion criteria. The Italian Medicines Agency (AIFA) reported that the results did not highlight any benefit linked to the early administration of tocilizumab in patients with COVID-19 pneumonia and the study was terminated early (32). The authors suggest that the results should be hypothesis- generating given the significant limitations associated with this study including missing data and study design (1).

EMPACTA (6)

The EMPACTA (Evaluating Minority Patients with Actemra) study finding contrast with the results from the COVACTA study. The EMPACTA study was a multicentre, randomized, double-blinded, placebo-controlled trial phase III trial which evaluated the efficacy and safety of tocilizumab 8 mg/kg IV (maximum dose of 800 mg) compared with a placebo in combination with SOC in hospitalized participants with COVID-19 associated pneumonia. Key inclusion criteria were hospitalized patients with COVID-19 pneumonia confirmed using the WHO criteria (including a positive PCR of any specimen, i.e., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan and SpO_2 <94% while on ambient air who did not require non-invasive or invasive mechanical ventilation, and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids as dictated by local treatment guidelines (a dose of no more than 1 mg/kg methylprednisolone or equivalent for no more than 5 days) and supportive care. Patients in whom, in the opinion of the treating physician, progression to death was imminent and inevitable within the next 24 hours, irrespective of the provision of treatments, were excluded from the study. The study population reflected patients that were often underrepresented in clinical trials largely from minority racial and

ethnic groups across the Americas and Africa. In total, 84% of the patients in the EMPACTA trial were Hispanic or Latino, Black, or American Indian or Alaska Native.

The primary endpoint was the cumulative proportion of patients requiring mechanical ventilation by Day 28 or death. Key secondary endpoints included time to improvement of clinical status, time to clinical failure; defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first, mortality rate by Day 28, time to discharge, and adverse events.

The results demonstrated that the addition of tocilizumab to SOC reduced the risk of progression to mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28 among hospitalised patients with COVID-19 pneumonia. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% (95% CI, 8.5% to 16.9%) in the tocilizumab group and 19.3% (95% CI, 13.3% to 27.4%) in the placebo group. The results suggested that patients in the tocilizumab arm were 44% less likely to progress to mechanical ventilation or death by Day 28 compared to patients who received placebo plus standard of care (HR =0.56 95% CI 0.32 to 0.97, P=0.04), however the effect estimate is highly uncertain. The broad confidence interval reported for the primary efficacy outcome analysis limits our certainty regarding the precision of the treatment effect associated with tocilizumab relative to placebo due to the small study sample. Studies with larger sample sizes could address our ability to understand the treatment effect associated with tocilizumab with greater precision in COVID-19. Tocilizumab did not reduce a number of key secondary outcomes including time to discharge, improvement in clinical status or all-cause mortality. Death from any cause by day 28 was numerically higher in the tocilizumab arm versus those in the placebo group; 10.4% of the patients in the tocilizumab group and 8.6% of those in the placebo group (weighted difference, 2.0%; 95% CI, –5.2% to 7.8%). At Week 4, rates of infections and serious infections were 10% and 5% in the tocilizumab arm and 11% and 6.3% in the placebo arm, respectively. The EMPACTA study did not identify any new safety signals for tocilizumab.

COVACTA (5)

The COVACTA study is a randomized, double-blind, placebo-controlled, phase III study of tocilizumab in hospitalized adult patients with *severe COVID-19* associated pneumonia have been published but have not been peer-reviewed. In total 452 patients were randomized to receive a single dose of tocilizumab 8 mg/kg IV (maximum dose of 800 mg) or placebo along with current standard of care (SOC). One additional dose of tocilizumab could be given 8- 24 hours after the initial infusion if the clinical signs and symptoms worsened or did not improve, defined as worsened ordinal scale clinical status or persistent fever. SOC was defined as per local practice and may have included antivirals, low-dose steroids, convalescent plasma and supportive care. Key eligibility criteria were hospitalized patients with COVID-19 pneumonia confirmed using the WHO criteria (including a positive PCR of any specimen, i.e., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan and SPO_2 ≤93% or PaO_2/FiO_2 <300mmHg. The primary endpoint was Clinical Status Assessed Using a 7-Category Ordinal Scale [Time Frame: Day 28] which tracked patients' clinical status based on the need for intensive care and/or ventilator use, as well as supplemental oxygen requirements. Secondary endpoints included the difference in mortality, mechanical ventilation, time to hospital discharge and additional ICU variables at Week 4. An interim analysis was conducted indicating that the COVACTA trial had failed to reach its primary or secondary endpoints. The odds ratio for clinical status improvement at four weeks did not differ significantly between the study arms (odds ratio= 1.19, 95% CI 0.81 - 1.76, p=0.36). Mortality at 28 days was 19.7% in the tocilizumab and 19.4% in the placebo group (p= 0.9410) and there was no significant difference in median time to hospital discharge

or ventilator free days between study arms. It is noted that patients in the placebo arm received higher levels of concomitant treatment with steroids both at baseline and during the trial (28.5% and 52.1%) 33.7%), than the tocilizumab arm (19.4% and 33.7%) during the study, however the imbalance is unlikely to have introduced bias towards lower mortality in the placebo arm as the mortality rate was higher in patients who received steroids in both study arms than in patients who did not received steroids, which is contrary to the known survival benefit associated with steroid use in COVID-19 (5,33). Median CRP levels were 157.2 (1.1 to 446.6) mg/L in the tocilizumab arm and 150.3 (1.6 to 499.6) mg/L in the SOC arm.

Veiga et al 2021 (4)

An open-label randomized trial in Brazil failed to detect a clinical or mortality benefit among 129 patients with *severe or critical COVID-19* who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (D dimer >2.74 nmol/L, CRP >50 mg/L, ferritin >300 µg/L, or lactate dehydrogenase greater than the upper limit of normal). More patients in the tocilizumab group were using supplementary oxygen at enrolment (60% *v* 44%), whereas use of non-invasive ventilation or high flow oxygen through a nasal cannula was higher in the control group (23% *v* 41%). Standard of care was defined according to local institutional guidelines. In total 84% in the tocilizumab arm and 89% in the SOC arms received concomitant corticosteroids. Adding tocilizumab to SOC when compared with SOC alone did not reduce the risk of mechanical ventilation or death at 15 days (28 versus 20 percent, OR 1.54, 95% 0.7-3.7), and there was a trend toward higher 28-day mortality with tocilizumab (21 versus 9 percent, OR 2.7, 95% CI 0.97-8.35). Two patients in the control arm received tocilizumab which was at the discretion of the treating physician. (4).

REMAP-CAP (8)

Results from the REMAP-CAP study, an open-label international randomized trial of 803 adult patients with *severe COVID-19* who were admitted to the intensive care unit and required either respiratory or cardiovascular support to receive one of two IL-6 inhibitors tocilizumab (8mg/kg) or sarilumab (400mg) or SOC. All patients were enrolled within 24 hours of admission to the intensive care unit. More than 80% of patients received concomitant glucocorticoids at enrolment or within the following 48 hours. 32.8% of patients randomised also received remdesivir. All but three patients were receiving respiratory support at the time of randomization, including high flow nasal oxygen (28.8%), non-invasive (41.5%) and invasive (29.4%) mechanical ventilation. Baseline patient characteristics including age, ethnicity and pre-existing co-morbidities were well balanced across both tocilizumab and SOC arms, however most important differences were accounted for by the covariate adjustment in the primary and secondary analyses (8).

The primary outcome was an ordinal scale combining in-hospital mortality (assigned −1) and days free of organ support to day 21. The primary analysis of organ support-free days (OSFD) and in-hospital mortality used data from all participants enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least one domain, adjusting for age, sex, time period, site, region, domain and intervention eligibility and intervention assignment. Median organ (respiratory and cardiovascular) support-free days were 10 (interquartile range [IQR] -1 to 16), 11 (IQR 0 to 16) and 0 (IQR -1 to 15) for tocilizumab, sarilumab and SOC groups. Compared with SOC, the median adjusted OR was 1.64 (95% CrI 1.25 to 2.14) for tocilizumab and 1.76 (95% CrI 1.17 to 2.91) for sarilumab, yielding >99.9% and 99.5% posterior probabilities of superiority suggesting a treatment benefit associated with tocilizumab. Tocilizumab (n = 353) and sarilumab (n = 48) were shown to reduce 28 day in-hospital mortality compared with SOC (28% and 22% versus 36%; OR for hospital survival 1.64, 95% CrI 1.14 to 2.35 for tocilizumab and 2.01, 95% CrI 1.18 to 4.71 for sarilumab, yielding 99.6% and 99.5% posterior probabilities of superiority. The treatment benefit associated with tocilizumab

appears to be consistent across both domains within the composite endpoint; tocilizumab is both preventing death and reducing ICU stay. The authors report that the estimates of treatment effect are greater in those treated with the combination of IL-6 therapy and corticosteroids over IL-6 treatment alone. The authors report that the estimates of treatment effect are greater in those treated with the combination of IL-6 therapy and corticosteroids over IL-6 treatment alone. However, the REMAP-CAP trial was not powered to compare tocilizumab with corticosteroids to tocilizumab without corticosteroids. Given the small proportion of patients treated with tocilizumab monotherapy alone in the REMAP-CAP study, it is difficult to characterise both the interaction effect or the combination effect of tocilizumab plus corticosteroids, however their analysis suggests that the combination of tocilizumab and corticosteroids as part of SOC is additive.

Survival follow up is also sufficiently long enough to conclude that those who are discharged from ICU remain alive. The difference in median organ support-free days may be misleading as all deaths are assigned a score of -1 for those who die in hospital. The difference in median organ support-free days should not be misinterpreted as a reduction in ICU support in terms of ICU capacity, particularly given that the study did not detect a difference in median ICU stay (adjusted median HR: 1.42, 95% CrI 1.18 to 1.70) between the tocilizumab and SOC arms among survivors.

A pre-specified sensitivity analysis of the primary outcome for the comparison between tocilizumab (n=353) and SOC (n=402) arms was conducted based on three CRP terciles subgroups. The cut off for the CRP terciles were 102 and 187 mg/L. It is unclear why these cut offs were applied. CRP lowest tercile reported median adjusted OR of the primary outcome: 1.45, 95% CI 0.85 to 2.48 and a 91.3% probability of superiority to control. The CRP middle tercile reported median adjusted OR of the primary outcome: 1.49, (95%CI 0.89 to 2.49) and a 93.5% probability of superiority to control. CRP highest tercile reported median adjusted OR of the primary outcome: 1.92 (1.12 to 3.34) and a 99.1% probability of superiority to control. Beneficial effects of tocilizumab across all CRP subgroups were demonstrated in this subgroup analysis of critically ill patients. However, a larger benefit with tocilizumab was noted in patients with highest tercile of CRP (≥187 mg/L) levels at study inclusion. The results from the REMAP-CAP study are consistent with the RECOVERY trial results, whereby benefit was noted in all CRP tercile subgroups but greatest in patients with highest tercile of CRP (≥187 mg/L) levels at study inclusion (7,8).

The reasons for the differences in treatment efficacy findings on mortality benefit between the REMAP-CAP and earlier RCTs are uncertain. Overall mortality rates in earlier RCTs were lower, suggesting a more severely ill population in the REMAP-CAP trial. The authors report that it is possible that IL-6 inhibitors can benefit a select group of critically ill patients who are treated early (e.g. within 24 hours of commencing organ support in an ICU) in the course of critical illness.

There were nine serious AEs reported in the tocilizumab group including one secondary bacterial infection, five bleeds, two cardiac events and one deterioration in vision. There were 11 serious adverse events in the control group, four bleeds and seven thromboses; and no serious adverse events in the sarilumab group. However, there no increased rates of serious adverse events reported.

RECOVERY (pre-print and not peer reviewed) (7)

The RECOVERY trial was an open label, randomised controlled adaptive platform trial which evaluated the safety and efficacy of multiple treatments for COVID-19. The tocilizumab vs. standard of care (SOC) arm included adult patients admitted to hospital with severe COVID-19 who displayed evidence of progressive disease with evidence of both hypoxia (SpO_2 <92% on room air or requiring O_2 therapy) and evidence of systemic inflammation (CRP ≥75 mg/L). CRP was chosen as a biomarker for inflammation given its wide use, correlation with serum IL-6 and early clinical studies in COVID-19

which report it to be associated with severity and prognosis. A CRP cut-off of 75mg/L for trial inclusion/exclusion was applied based on a publication by Ruan et al 2020 and other studies (34–39). At randomisation, 562 (14%) patients were receiving invasive mechanical ventilation, 1,686 (41%) were receiving non-invasive respiratory support (including high-flow nasal oxygen, continuous positive airway pressure, and non-invasive ventilation), and 1,868 (45%) were receiving no respiratory support other than simple oxygen therapy (9 of these patients were reportedly not receiving oxygen at randomisation).

A total of 2,022 patients were randomly allocated to receive tocilizumab by intravenous infusion and were compared with 2,094 patients randomly allocated to SOC alone. Those randomised to tocilizumab received an intravenous dose up to 800 mg (depending on weight). A second dose could be given 12 to 24 hours later at the discretion of the treating physician. SOC included corticosteroids for COVID-19 patients requiring treatment with oxygen. Participants and local study staff were not masked to the allocated treatment. The steering committee, investigators, and all others involved in the trial were masked to the outcome data during the trial. (7)

Baseline patient characteristics including age, ethnicity and co-morbidities were well balanced across both arms. There was a slightly greater proportion of males recruited to the SOC arm (69%) relative to the tocilizumab arm (66%). COVID-19 disease characteristics including degree of respiratory support (no ventilator support, non-invasive and invasive ventilator support), biochemistry (CRP, ferritin and creatinine) and co-morbidities at baseline were also well balanced across both treatment arms. Median CRP was 143 [IQR 107-204] mg/L and 82% of patients across both treatment arms were receiving systemic corticosteroids at randomisation.

The primary outcome was 28-day mortality, assessed in the intention-to-treat population [1]. Tocilizumab was shown to reduce the relative risk of death from COVID-19 at day 28 by 14% (RR: 0·86; 95% CI 0·77 to 0·96; p=0·007) and the absolute risk of mortality by 4%; 596 (29%) of the 2022 patients randomised to tocilizumab and 694 (33%) of the 2,094 patients allocated to usual care died within 28 days. Consistent results of the primary outcome were seen in all pre-specified subgroups including age, gender, ethnicity, level of respiratory support, days since symptom onset, and in patients on systemic corticosteroids. A clear mortality benefit was seen in those receiving systemic corticosteroids; the effect size of tocilizumab when combined with systemic corticosteroids (28-day mortality RR =0.80, 95% CI 0.70 to 0.90) is larger than reported in the overall study results (28-day mortality RR: 0.86, 95% CI 0.77 to 0.96, p=0.007) which included patients who did not receive systemic corticosteroid therapy (n=357/2022 (18%) in the tocilizumab arm, n=367/2094 (18%) in the SOC arm). The mortality benefit was not seen in patients receiving tocilizumab monotherapy (RR: 1.16, 95% CI 0.91- 1.48). Statistically there is an interaction effect between tocilizumab and corticosteroids. However it is not clear if this interaction effect is a statistical effect due to for example frailty or survival bias or whether this is a clinical interaction whereby patients do better when on combined treatment. The evidence from the subgroup analysis of patients on corticosteroids indicates that patients who are not on corticosteroids do not derive a survival benefit (as per the primary outcome) from tocilizumab.

Secondary outcomes were time to discharge alive from hospital, and the use of invasive mechanical ventilation (including extra-corporeal membrane oxygenation (ECMO)) or death among patients not receiving invasive mechanical ventilation baseline. Tocilizumab increased the probability of discharge

[1] For this preliminary report, information on the primary outcome is available for 92% of patients. This is expected to increase to >99% by early March when all patients have passed the 28-day follow-up period.

from hospital alive within 28 days from 47% to 54% (RR: 1.22, 95% CI 1.12 to 1.34, p<0·0001). These benefits were reported as observed in certain patient subgroups, including those requiring oxygen via a simple face mask (RR:1.2, 95% CI 1.09 to 1.37) or non-invasive ventilation (RR: 1.23, 95% CI: 1.06 to 1.43) but not invasive mechanical ventilation (RR:1.16, 95% CI 0.78 to 1.74) at randomisation. The Review Group highlight There is a pre-planned analysis at 6 months that will provide information on long term outcomes given that median hospitalisation length of stays are >28 days for patients with COVID-19. Among patients not on invasive mechanical ventilation at baseline, tocilizumab was shown to significantly reduce the chance of progressing to invasive mechanical ventilation or death when compared with SOC alone (absolute difference 38% to 33%, RR:0·85, 95% CI 0·78 to 0·93, p=0·0005). This effect was observed in those not on respiratory support (RR:0.82, 95% CI: 0.69 to 0.96) or non-invasive ventilatory support (RR:0.89, 95% CI: 0.80 to 0.98) at baseline. Other clinical endpoints evaluated in the RECOVERY trial indicate that there was no evidence that tocilizumab had any effect on the chance of successful cessation of invasive mechanical ventilation. Although the authors did not report any effect on the duration of invasive mechanical ventilation, the study was not powered to detect any effect. The use of haemodialysis or haemofiltration was lower in the tocilizumab arm (n=103/2003, 5%) than in the SOC arm (n=142,2075, 7%) (RR: 0.75, 95% CI 0.59 to 0.96, p=0.02).

Following random assignment, seventeen per cent of patients in the tocilizumab arm did not receive treatment with tocilizumab. The study authors could not provide an explanation for this citing that the reason patients did not receive treatment with tocilizumab was not recorded. It is also noted that the authors do not report the timing from admission and onset of hypoxia to administration of tocilizumab, which limits our ability to characterise the timing and sequence of events prior to administration of tocilizumab.

Prespecified safety outcomes included cause-specific mortality and major cardiac arrhythmia. Preliminary information on cause-specific mortality shows no evidence of an increase in cause-specific mortality from other infections and no differences in the frequency of new cardiac arrhythmias. There were three reports of serious adverse reactions believed to be related to tocilizumab: one each of otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess, all of which resolved with standard treatment.

Observational studies

Overall, observational studies published to date have suggested that tocilizumab may improve the outcomes of patients with severe or critical COVID-19 infections. However, the body of evidence published are predominantly single centre, non-randomised studies with small sample sizes of suboptimal methodological quality which are prone to various biases and structural limitations. As such these are not as informative as well designed controlled RCT studies. Unlike randomised comparisons, observational studies cannot be used to draw causal inferences because of inherent known and unknown confounders which affect the results generated and our ability to interpret the results. Generally, observational studies included in this review have lacked the standard steps taken to minimise confounding such as prospective design, statistical adjustment for prognostic factors including propensity score matching, or stratification. Where statistical methods were employed to control for known confounders, unmeasured confounding cannot be ruled out. Observational studies assessed in this review have also highlighted that that key confounding factors are not always collected in a standardised way and there are often inconsistencies in terms of how data are classified and how missing data are handled.

There are limited observational data to suggest that tocilizumab may have a beneficial effect on clinical outcomes and survival if administered to patients outside of the ICU setting in the earlier stages of

COVID-19 pneumonia (40–43). The definition of early stages of COVID-19 is study dependent as the aetiopathophysiology has not been elucidated to date. Some studies suggest that treatment with tocilizumab in patients with features of a cytokine storm may prevent progression to mechanical ventilation or death when compared against standard of care (17,42,44–46). In an observational study of 186 hospitalised patients with severe COVID-19 treated with tocilizumab through a compassionate use programme in Madrid, Spain, Gorgolas *et al* report that tocilizumab was more effective when administered to patients whose oxygen support was less than FiO_2 ≤0.5%, than when administered in more advanced stages of COVID-19 (FiO_2 >0.5%), with patients achieving lower rates of intubation or death (13% vs 37% respectively, p<0·001). However, it is noted that patients (n=21) who died within 24 hours after tocilizumab administration were excluded from the final analysis. The dose and timing of administration of tocilizumab was variable and clinical decisions regarding a patient's eligibility for intubation were decided by the hospital's committee; those with more severe disease are more likely to be intubated than those with less severe disease. It is also noted that the majority of patients (>90%) received concomitant treatment with low molecular weight heparin, and corticosteroids which may have influenced the study results (47).

In a retrospective analysis of 544 patients with severe COVID-19 in two centres in Italy, Guaraldi *et al* also report that tocilizumab may reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia. All patients were treated with the standard of care (i.e., supplemental oxygen, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin), and a non-randomly selected subset of patients also received tocilizumab. After adjusting for sex, age, recruiting centre, duration of symptoms, and baseline Sequential Organ Failure Assessment (SOFA) score, intravenous or subcutaneous tocilizumab (n=179) was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p=0·020) versus standard of care treatment (n=365) (48). However, the lack of treatment concealment associated with tocilizumab in this open label study may have led to variability in clinical decision making which can bias treatment outcomes reported in this study e.g. in a decision of when to move a patient to invasive ventilation or when progression to death/ ICU is imminent irrespective of the provision of treatments. In a single-arm, prospective, multicentre open label study of 63 hospitalised adult patients with severe COVID-19 in Italy, Sciascia *et al* report that tocilizumab administration within 6 days of admission to the hospital was associated with an increased likelihood of survival when compared with the administration of tocilizumab after the 7th day of admission (HR 2.2 95%CI 1.3 to 6.7, p<0.05) in patients (n=63) with severe COVID-19 (41). Tocilizumab was administered intravenously (n=34/65) or subcutaneously (n=29/65). The choice of route of administration of tocilizumab was based on drug availability only. The administration schedule including the timing, dosing and frequency of administration of tocilizumab was also unclear which may impact on outcomes, particularly when there are still questions regarding the appropriate time point of the disease course in which tocilizumab may confer benefit. The authors also do not report any clinical or laboratory prognostic variables which may aid the identification of patients in whom tocilizumab may confer benefit within the 6-day window of admission.

Gupta *et al* report the results from STOP-COVID, an US observational study of 4,485 adult COVID-19 patients admitted to ICUs at 68 U.S.-based hospitals from March 4th through May 10th 2020. The investigators report that the risk of in-hospital mortality was lower in patients treated with tocilizumab in the first 2 days of ICU admission compared with patients whose treatment did not include early use of tocilizumab. Patients were stratified by whether they received tocilizumab during the first two day of ICU admission. The main outcomes were time to death and 30-day mortality. The final analysis included 3,924 patients (median age, 62 years; 62.8% were male), of whom 433 (11%) received tocilizumab. There were 1,544 deaths: 125 in the tocilizumab group and 1,419 in the no tocilizumab

group (28.9% vs. 40.6%). Median follow-up was 27 days (IQR, 14-37), during which time tocilizumab patients had a lower mortality risk compared to with those not treated with tocilizumab (HR =0.71; 95% CI: 0.56 to 0.92). The estimated 30-day mortality was 27.5% (95% CI: 21.2% to 33.8%) in the tocilizumab-treated patients and 37.1% (95% CI: 35.5% to 38.7%) in the non-tocilizumab-treated patients (risk difference, 9.6%; 95% CI: 3.1% to16.0%). However, the authors acknowledge that the results should be considered preliminary until conclusive evidence is obtained from RCTs, due to the inherent susceptibility of observational studies to unmeasured confounding (49). Of note the study did not control for or collect any data on concomitantly administered medications including corticosteroids. Other studies have reported that there is no treatment benefit associated with tocilizumab in the severe COVID-19 disease setting.

A recently published systematic review and meta-analysis (which pre-dates the publication of the RECOVERY and REMAP-CAP studies) reports that there is no conclusive evidence that tocilizumab provides any additional benefit to patients with severe COVID-19 when compared to placebo or control cohorts in terms of all-cause mortality, requirement for mechanical ventilation or risk of ICU admission (11). Colaneri *et al* report an analysis of critically ill patients with COVID-19 pneumonia who were prospectively enrolled in the SMAtteo Covid19 Registry (SMACORE) in Italy. Patients treated with tocilizumab (n=21) were matched using propensity scoring to patients treated with standard of care (SOC) (n=21). Both groups were treated with SOC which included a combination of hydroxychloroquine, azithromycin and a prophylactic dose of low molecular weight heparin. The authors report that the addition of tocilizumab did not significantly affect risk of ICU admission (OR 0.11; 95% CI 0.00 to 3.38; p = 0.22) or 7-day mortality rate (OR 0.78; 95% CI 0.06 to 9.34; p = 0.84) when compared with SOC in critically ill patients with severe COVID-19 pneumonia (50). Although the authors attempted to reduce bias through propensity score matching, unmeasured confounding cannot be ruled out as this procedure is unable to control for the effect of variables not included in the model which may be significant, given that the pathophysiology of COVID-19 is still unclear. The results of this study suggest that tocilizumab did not affect the risk of ICU admission or mortality rate in a cohort of 21 patients. However, this is a single centre, observational study with a small sample size, which could have limited the power of the analyses, and should not be extrapolated to conclude an absence of treatment effect. Price *et al* report the results of a single centre, retrospective observational study of patients with severe (n=94) and non-severe (n=59) COVID-19 treated with tocilizumab in a hospital in Connecticut, USA, guided by a hospital-based treatment algorithm that initially focused on patients with severe disease but evolved to target CRS. The authors hypothesised that patients treated for CRS, irrespective of disease severity (severe, ≥ 3 L supplemental oxygen to maintain oxygen saturation > 93%) at the time of admission, would have improved outcomes and that tocilizumab-treated patients with severe disease would have survival outcomes more like patients with less severe disease. Tocilizumab-treated patients with severe disease had higher baseline admission levels of high-sensitivity C-reactive protein (120 vs 71 mg/L; p = < .001) and received tocilizumab sooner (2 vs 3 days; p = < 0.001), but their survival was similar to that of patients with non-severe disease (83% vs 91%; p = 0.11), suggesting that the treatment of CRS with tocilizumab, rather than disease severity at admission, may play a key role in survival. The authors also observed that D-dimer levels increased in tocilizumab-treated patients and suggested that IL-6 receptor antagonism may interrupt only part of the hyperinflammatory response of CRS (51). A key limitation of this study includes the potential confounding from concomitant administration of glucocorticoids which was higher in the severe group (35%) than in the non-severe group (8.9%) which may have impacted on the reported treatment outcomes. The results should be considered preliminary, as they are from an uncontrolled series and a causal inference cannot be established. Of note, in a non-peer reviewed study, Marfella *et al* highlight their experience of tocilizumab in hyperglycaemic patients suggesting reduced effects relative to normoglycemic patients due to the higher baseline and persistent plasma IL-6 levels (52). Several case reports/series of interest report the

experience of tocilizumab in renal transplant and liver transplant patients (53,54). However, these are single case observations and cannot be extrapolated as an indication or absence of treatment effect.

Timing and route of administration of tocilizumab

The timing of administration of tocilizumab in relation to disease course remains uncertain and remains to be established. The results from the REMAP-CAP and RECOVERY study suggest that evidence of systemic inflammation as defined by CRP ≥ 75 mg/L and evidence of hypoxaemia should guide the identification and selection of patients with COVID-19 in whom tocilizumab in combination with systemic corticosteroids and SOC will offer mortality and other treatment outcome benefits irrespective of the level of respiratory support. There are conflicting conclusions as to whether treatment setting impacts on whether tocilizumab in combination with systemic corticosteroids offers treatment benefit. In contrast with the results from the REMAP-CAP study, the RECOVERY trial did not find any dependence between efficacy of tocilizumab and either timing of hospitalisation from symptom onset or that ICU admission was a requirement to demonstrate evidence of treatment benefit. Furthermore, no absolute cut off in terms of number of days of symptoms has been robustly identified in the RECOVERY trial to suggest that the timing of administration of tocilizumab from symptom onset has an impact on important patient outcomes including mortality, disease progression or organ support(7,8). Studies published to date have not yielded any robust or conclusive evidence supporting an optimal timing of administration of tocilizumab in COVID-19 when guided by IL-6 levels. Clinical decisions regarding the timing to administer tocilizumab in retrospective observational cohort studies published to date highlight that decisions to treat have been predominantly driven by clinical parameters and biomarkers assumed to indicate IL-6-mediated immunopathology rather than being driven by a range or threshold of serum IL-6 levels.

Most studies in COVID-19 report that tocilizumab has been administered intravenously at a dose of 4-8mg/kg to patients with COVID-19 in line with its product licences for CAR-T cell induced CRS. More recently, some case reports have reported the use tocilizumab administered subcutaneously. Although there are data showing similar efficacy of tocilizumab administered intravenously or subcutaneously in rheumatoid arthritis, the pharmacokinetic and pharmacodynamic profile of tocilizumab in CRS is not well described. It is unclear whether the subcutaneous and intravenous routes of administration are interchangeable (55,56).

Safety of tocilizumab

There are limited safety data available for tocilizumab in this setting. Some studies have reported no increased risk of infection or adverse events (AEs) associated with tocilizumab (50,68). Other studies have suggested that treatment with tocilizumab might favour the persistence of the SARS-CoV-2 virus and iatrogenic infections (45). Kimmig *et al* reported that tocilizumab was associated with a higher incidence of secondary bacterial infections including hospital-acquired pneumonia and ventilator associated pneumonia (64.3% vs. 31.3% p=0.010) in critically ill COVID-19 patients. However, it is plausible that patients receiving tocilizumab were sicker, had a worse prognosis and therefore more likely to acquire a secondary infection (57). Some case studies reported a potential risk of elevated hepatic enzymes and two cases of acute large bowel perforation in patients with COVID-19 pneumonia who received empiric tocilizumab (42,58). Preliminary data from the RECOVERY trial (non-peer reviewed) did not identify any new safety signals and the preliminary analysis of the safety data suggests that there are no evidence of an increase in cause-specific mortality from other infections and no differences in the frequency of new cardiac arrhythmias. The evidence (yet to be peer reviewed) from the REMAP-CAP study also reported that there were no increased rates of serious AEs reported. The COVACTA indicated that there were similar proportions of patients experiencing AEs

and serious AEs in the tocilizumab and SOC arm. Rates of infections were lower in the tocilizumab arm relative to SOC; rates of infections at 28 days were 38.3% and 40.6% in the tocilizumab and placebo arms, respectively, and the rates of serious infections were 21.0% and 25.9% in the tocilizumab and placebo arms, respectively. Of note, there was only one case of an opportunistic infection in the tocilizumab (*Candida* sepsis) and SOC (respiratory moniliasis) arms. The COVACTA study did not identify any new safety signals for tocilizumab (5). The EMPACTA study did not identify any new safety signals for tocilizumab. Salvarini et al from the RCT-TCZ-COVID-19 Study Group did not note any treatment related severe AEs associated with tocilizumab. The most common AEs reported were increased alanine aminotransferase level and decreased neutrophil count (9). Data from the CORIMUNO-TOCI-1 did not identify any new safety signals and no increase in adverse or serious AEs. The investigators report a lower rate of serious infections (n=2 in the tocilizumab arm, n=11 in the SOC arm) despite decreased neutrophil count and increased rate of neutropenia in the tocilizumab arm and suggest that these results might be explained by the decreased frequency of transfer to the ICU, and the more frequent use of steroid treatment (2).

Treatment guidelines

Treatment Guidelines which recommend the use of tocilizumab in COVID-19 which have been updated since October 2020.

The National Institute for Health (February 3, 2021) recommend that for patients who are within 24 hours of admission to the ICU and who require invasive or non-invasive mechanical ventilation or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19. For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab or sarilumab for the treatment of COVID-19, except in a clinical trial (59).

The Infectious Disease Society of America (22nd February 2021) recommend that among hospitalized adults with progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence).

- *Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.
- **Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

Version 16 (9th February 2021) of the Belgian guidelines recommend that interleukin (6 or 1) blockers should only be used in clinical trials (60,61).

The Medicines Health and Regulatory Agency (UK medicines regulatory body) (17th February 2021) released an Interim Clinical Commissioning Policy for tocilizumab in critically ill patients with COVID-19 pneumonia (adults). They suggest that tocilizumab is recommended to be available as a treatment option through routine commissioning for adult patients (aged 18 years and older) hospitalised with

COVID-19 who meet all eligibility criteria and none of the exclusion criteria. Hospitalised patients are eligible[1] to be considered for tocilizumab if:

- COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis; and
- They are receiving (or have completed a course of) dexamethasone or an equivalent corticosteroid unless contraindicated; and
- With a C-reactive protein level of at least 75mg/L; AND an oxygen saturation of <92% on room air OR requirement for supplemental oxygen; OR
- If an IL-6 inhibitor has not been already administered for COVID-19 during this admission and within 24-48 hours of commencement of respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation).

Exclusion criteria includes –

- Known hypersensitivity to tocilizumab.

Cautions:

- Co-existing infection that might be worsened by tocilizumab,
- A baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal (caution is recommended if hepatic enzymes are more than 1.5 times the upper limit of normal)
- A pre-existing condition or treatment resulting in ongoing immunosuppression.

A single dose is to be administered. A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximise available supply (62).

A single dose is to be administered. A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximise available supply.

[1] The decision to initiate treatment with tocilizumab should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty.

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Appendix 1: Search strategy

A targeted literature review was conducted to inform the Rapid Evidence Review based on a search strategy developed by the Information Specialist at the National Centre for Pharmacoeconomics. A typical hierarchy of evidence was considered in the search, from highest to lowest:

- Systematic Literature Reviews and meta-analyses
- Randomised Controlled Trials
- Observational studies
- Published expert opinion

The landscape Review of International Clinical Guidelines identified up-to-date guidelines predominantly from other European countries and also China, the initial epicentre of the COVID-19 pandemic. Clinical trial registers in the EU, US and China were searched for evidence of ongoing or completed clinical trials.

Source	**Search**
Pubmed	(2019-nCoV OR 2019nCoV OR COVID-19 OR SARS-CoV-2 OR ((Wuhan AND coronavirus) AND 2019/12[PDAT]:2030[PDAT])) AND ((((("tocilizumab" [Supplementary Concept]) OR "Antibodies, Monoclonal, Humanized"[Mesh]) OR "Interleukin-6"[Mesh] OR IL-6 OR IL6))
LitCovid	"Tocilizumab" OR "Interleukin-6" or "IL-6"
MedRxiv	"Tocilizumab" OR "Interleukin-6" or "IL-6"
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) AND “Tocilizumab”