Rapid Evidence Review

Tocilizumab in the management of patients who have severe COVID-19 infection with suspected hyperinflammation.

Version 3, 20th May 2020

National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

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Key changes (highlighted in yellow) between version 2 (10th April 2020) and version 3 (20th of May 2020): Updated evidence (n=27 publications) relating to tocilizumab in COVID-19 added.

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

Emerging correlative evidence supports the view that hyperinflammation plays a key role in the pathogenesis of severe COVID-19. Elevated inflammatory markers including IL-6 levels have been described in patients with severe COVID-19. Recently, two meta-analyses examined the role of IL-6 in COVID-19 and concluded that IL-6 levels are significantly elevated in patients with COVID-19 and are associated with adverse clinical outcomes. Extrapolation of evidence from cytokine-driven hyperinflammatory related disorders suggests that patients who have severe COVID-19 with hyperinflammation could benefit from tocilizumab. Preliminary unpublished results from a multicentre, open-label, randomized, controlled trial (CORIMUNO-TOCI) in France which is evaluating tocilizumab for the treatment of moderate or severe COVID-19 pneumonia have reported a significantly lower proportion of patients requiring ventilator (non-invasive and mechanical) or death at day 14 in the tocilizumab arm however the study and efficacy and safety results have not been published or peer reviewed . Several small single-arm observational studies and retrospective case series/reports suggest that tocilizumab may be of benefit in patients with COVID-19 exhibiting signs of cytokine release syndrome (CRS), however there is still no definitive evidence supporting the routine use of tocilizumab in severe COVID-19. Furthermore, emerging evidence on the role of IL-6 suggests that the timing of administration the treatments for hyperinflammation is of critical importance. A preliminary report from Italy suggests that treatment with tocilizumab in patients with features of a cytokine storm may be more effective outside of the ICU setting in non-ventilated patients to prevent cytokine storm evolution. However, the timing of administration in relation to disease course remains uncertain.

Conclusion

Our Rapid Review finds that the evidence[1] on comparative efficacy is insufficient to conclude whether tocilizumab is efficacious in the management of hyperinflammation in patients with COVID-19. As the evidence continues to emerge for the use of tocilizumab in this setting, every effort should be made to collect relevant clinical outcomes.

[1]*Some of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or "preprints". These are preliminary reports which have not been subjected to peer-review – the conventional model for judging the quality of research. In the interests of speed and open access, the international scientific community has recognised the advantage of preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is also a greater potential for dissemination of low-quality research. The ERG critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.*

Rapid Evidence Review

Introduction

Tocilizumab is a humanised anti-IL6 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 (1). Interluekin-6 (IL-6) is a key pro-inflammatory cytokine that is elevated in CRS. Suppression of pro-inflammatory IL-1 family members and IL-6 have been shown to have a therapeutic effect in many inflammatory diseases, including viral infections (2). 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 (3,4). Tocilizumab prevents Il-6 from binding to soluble and cell associated Il-6 receptors inhibiting IL-6 mediated signalling (5).

Potential role of tocilizumab in COVID-19

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 are highlighting the characteristics of COVID-19 infected patients (6–9). Clinical data suggests that disease progression in COVID-19 infected patients may be driven by a dysregulated immune response resulting in a cytokine storm (10). Cytokine release syndrome (CRS) is a diverse set of conditions of pleotropic causation associated with the clinical phenotype of exuberant systemic inflammation, multi-organ failure, hyperferritinaemia and high mortality (11). The condition is associated with exuberant 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 (12). Several studies in patients with COVID-19 have reported higher levels of cytokines and chemokines (IL-1β, IL2, IL-6, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNFα), lymphopenia (in CD4+ and CD8+ T cells), and decreased IFNγ expression in CD4+ T cells, in patients with severe COVID-19 disease compared with mild disease, suggesting a possible association between a cytokine storm and COVID-19 disease severity (13–16). The pro-inflammatory cytokineIL-6 has been highlighted as playing a prominent role in the inflammatory cascade in COVID-19. Recently, two meta-analyses examined the role of IL-6 in COVID-19 and concluded 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 (17–19). Emerging evidence suggests 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). Tocilizumab has also shown efficacy for other iatrogenic causes of CRS and has demonstrated efficacy in and is licensed for the treatment of CAR-T cell associated CRS (12). The timing of administration of an anti-IL6-6R in the setting of CRS is considered crucial (21,22)

Screening for hyperinflammation in patients with COVID-19 in which tocilizumab may be efficacious

The pathogenesis of COVID-19 remains unclear and there is no clear understanding of the molecular events which precipitate a cytokine storm (23). The identification of a unique definition of CRS during COVID-19 infection is crucial to better customize the management of critical patients (24). 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. A correspondence from Mehta et al advocate active screening for hyperinflammation in patients with COVID-19 using H score (see Appendix 3) and trends in laboratory tests including increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate, to identify groups in whom targeted immunomodulation might improve mortality (10). However, Ritchie et al in further correspondence suggest that increased virus burden secondary to failure of the immune response to control infection drives inflammation; consequently, it is COVID-19 disease severity which requires correction, rather than the postulated hyperinflammation being an inappropriate host response. Ritchie et al further suggest that immunosuppression in patients with overwhelming viral illness therefore may be inadvisable as suppression of IL-6 could result in detrimental effects by inhibiting host antiviral and anti-microbial immunity, which could result in delayed virus clearance and perpetuate the COVID-19 illness and could promote secondary bacterial infection(25).

Timing and route of administration of tocilizumab

The timing of administration in relation to disease course remains uncertain. It is unknown if earlier administration of tocilizumab triggered by rising inflammatory markers could prevent or decrease severity of respiratory decompensation. Xu et al suggest that IL-6 concentrations can be detected in patients with persistent fever which lasts longer than 3 days. They suggest that treatment with tocilizumab could be considered in patients with high risk factors (undefined), in severe or critically ill patients with a serum IL-6 which is greater than 20 pg/ml (26). Results from a single Italian Centre observational study suggests that treatment with tocilizumab in patients with features of a cytokine storm may be more effective outside of the ICU setting in non-ventilated patients. Quartuccio et al suggest that randomised controlled trials should trials should target non-ICU patients prior to ventilation to prevent cytokine storm evolution (27). However, it is unknown if earlier administration of tocilizumab triggered by rising inflammatory markers could prevent or decrease severity of respiratory decompensation. The optimal timing of tocilizumab for COVID-19 remains to be established. Of note, the extreme elevation of IL-6 levels in the aftermath of tocilizumab administration has been described, due to increased availability of IL-6 resulting from less binding to the IL-6 receptor which suggests that IL-6 concentrations may not be a robust marker of disease activity in tocilizumab-treated patients (5). 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 licenses 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 (28,29).

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

Thirty-three studies have been identified from our search strategy (see Appendix 4) including observational studies (n=16) and case series/ reports (n=17). A rapid critical appraisal of the observational studies reporting the use of tocilizumab in COVID-19 was conducted by the ERG and are summarised in Appendix 1.

There are limited robust data to suggest that tocilizumab may have a beneficial effect on clinical outcomes and survival if administered in patients early during COVID-19 pneumonia (30–33). Some studies suggest that treatment with tocilizumab in patients with features of a cytokine storm may be more effective outside of the ICU setting to prevent progression to mechanical ventilation when compared against standard of care (27,34,35). Sciascia et al report that tocilizumab administration within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2 95%CI 1.3 to 6.7, p<0.05) in patients (n=63) with severe COVID-19 (31). However, these studies are limited by their retrospective nature, lack of control arm for comparison and potential confounding from concomitant administration of multiple drug anti-viral, anti-inflammatory and immunomodulatory therapies (31,33,36). Other studies reported more pessimistic results. Colaneri et al report that tocilizumab did not significantly affect 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 standard of care in critically ill patients with severe COVID-19 pneumonia (37). 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 (38). Several case reports/ series of interest report the experience of tocilizumab in renal transplant and liver transplant patients (39,40). However, these are single case observations and cannot be extrapolated as an indication or absence of treatment effect.

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 (31,41). Other studies have suggested that treatment with tocilizumab might favour the persistence of the SARS-CoV-2 virus and iatrogenic infections (27). 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 (42).

The observational studies reporting the efficacy and safety profile of tocilizumab in COVID-19 are predominantly single centre, non-randomised studies with small sample sizes which are prone to various biases and structural limitations. This limits our ability to ascertain the safety and efficacy profile of tocilizumab in COVID-19. While we await the results of randomised controlled trials, well-designed, protocol driven prospective observational studies may be informative. The ERG is aware of a press release from the Paris university hospital trust (AP-HP) which announced preliminary unpublished results from a multicentre, open-label, randomized, controlled trial (CORIMUNO-TOCI) in France. The study is evaluating tocilizumab for the treatment of moderate or severe COVID-19 pneumonia. Patients with moderate or severe COVID-19 pneumonia not requiring intensive care upon admission to hospital were recruited to the trial. The primary composite outcome was need for ventilation (non-invasive or mechanical) or death at day 14. A total of 129 patients were recruited to the study where 65 patients were randomised to standard of care in combination with tocilizumab and 64 to standard of care alone. The AP-HP reported that a significantly lower proportion of patients reached the primary outcome in the tocilizumab arm (43). Results of this study are not yet available but are being submitted for publication in a peer-reviewed journal.

Treatment guidelines

Treatment Guidelines which recommend the use of tocilizumab in COVID-19

Guideline (Date published, version). Group	Patient population	Dosing, frequency and duration	Monotherapy or in combination	Supportive therapies
America Infectious Disease Society of America Treatment and Management of Patients with COVID-19 Last updated April 13th 2020	Patients who have been admitted to the hospital with COVID-19 (In a clinical trial setting only)	Not specified	Not specified	Not specified
National Institute of Health. Last updated May 12th	There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against any immunomodulatory therapy in COVID-19 patients with severe disease. There are insufficient data to recommend either for or against the use of IL-6 inhibitors (e.g., sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19 (AIII).	Not specified	Not specified	Not specified
Poland	Patient with respiratory failure, clinically unstable (MEWS score of 3-	8mg/kg (maximum 800mg) in a single dose (1-hour infusion)	In combination with remdesivir (loading dose 200mg on day one, maintenance dose of	Glucocorticoids are necessary when tocilizumab is used.

Version not specified. Date published 31/03/2020 Association of Epidemiologists & infectiologists	4) and in patients with elevated IL-6 concentration. Also indicated for primary treatment & in patients in critical condition with MEWS score >4		100mg for 10 days) and chloroquine (250mg BD for up to 10 days). If remdesivir not available use lopinavir/ritonavir (400/100mg BD for 28 days). If chloroquine not available use hydroxychloroquine (400mg BD loading dose, maintenance dose 200mg BD for 10 days)	Methylprednisolone IV 1mg/kg/day for 5 days, followed by 40mg per day for 3 days, and 10mg daily for 2 days. OR alternatively Dexamethasone IV, 20mg per day for 5 days, followed by 10mg daily for 3 days, followed by 5mg per day for 2 days.
Belgium 06 May 2020; Version 8 Belgian Task Force Group	Any use should be limited to clinical trials or within Belgian/international cohort studies if possible. May be considered on an individual bases in patients with persistent inflammation (i.e. elevated Il-6, CRP, D Dimers, or ferritin) and ARDS requiring mechanical ventilation with evidence of bacterial superinfection/sepsis	None provided	Not specified	Not specified
Italy Version not specified. Date published 17/03/2020 National Institute for Infectious Diseases	Patients affected by respiratory symptoms, clinical unstable, not in critical conditions (MEWS score 3-4 Critical patients (MEWS >4) Tocilizumab administration should be guided by the presence of 1 or more of following selection criteria: a) PaO2/FiO2 ratio <300mmHg; b) rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive	8mg/kg, max dose 800mg/kg, single intravenous over 1 hour; in absence or with poor clinical improvement, s second dose should be administered 8-12 hours later. PCR & D-dimer (±iL-6) after 24 hours from each administration.	In combination with antiviral therapy (either remdesivir, lopinavir/ritonavir, hydroxychloroquine or chloroquine	Steroids are mandatory if tocilizumab is used – Methylprednisolone 1mg/kg daily intravenously for 5 days, followed by 40mg daily for 3 days, and 10mg daily for 2 days or alternatively Dexamethasone 20mg daily intravenously for 5 days, followed by 10mg daily for 3 days and, 5mg daily for 2 days.

	ventilation; c) IL-6 levels >40ng/ml (if not available D-Dimer levels >1000ng/ml)			
Italy Version 2. Date published 13/03/2020 Italian Society for Infectious Disease (SMIT)	Patient positive for COVID-19 with co-morbid risk factors needing O2 therapy or rapid deterioration and a BCRSS# score Or Patient positive for COVID-19 with a severe pneumonia, ARDS or global respiratory insufficiency, haemodynamic failure, need for mechanical ventilation Inclusion criteria: - Duration of initial high COVID-19 viral load - Worsening of respiratory exchanges Elevated IL-6 levels (>40pg/ml); or high levels of D-dime (/or PCR &/or ferritin, &/or fibrinogen progressively increasing	a) Maximum 3 infusions at a dose of 8mg/kg body weight (Max dose infusion 800mg) b) Second infusion 8-12 hours after the first c) If partial or incomplete clinical response, POSSIBLE third infusion at 16-24 hours after first infusion Table of dose per body weight provided	In combination with remdesivir (where available) or alternative antiviral therapy Or In combination with remdesivir (where available) or alternative antiviral therapy and diagnosis of ARDS	Rule out other baseline systemic infections, potential to commence preventive broad-spectrum antibiotic therapy. Option to screen for MTB prior to treatment using the IGRA test (not necessary to have results).
Spain Version not specified. Date published: 28/03/2020 Ministry of Health Spain – COVID-19 Technical Documents for Healthcare Professionals – medical treatment	The proposed criteria are for tocilizumab use (in the absence of enrollment in a clinical trial: • Interstitial pneumonia with severe respiratory failure (score = 2); • Rapid respiratory worsening requiring non-invasive or invasive ventilation (score ≥ 3 on the COVID respiratory severity scale);	**Adult Dose** Administration at fixed doses according to the following treatment scheme: • Patients weighing ≥75 kg: **single dose** of 600 mg. • Patients weighing <75 kg: **single dose** of 400 mg.	Not specified	Not specified

	• Presence of extrapulmonary organic failure (mainly Shock or score ≥ 3 on the SOFA scale); • Criteria for severe systemic inflammatory response. In adults: elevated levels of IL-6 (> 40 pg / ml) (alternatively increasing levels of D-dimer (> 1500 ng / ml) or progressively increasing D-dimer. In pediatric patients, it is required the presence of high levels of IL-6 (> 40 pg / ml) (alternatively high levels of D-dimer (> 400 ng / ml) or progressively increasing D-dimer). • Patient who, according to his baseline clinical condition, would be an ICU admission subsidiary.	**Pediatric Dose** It is under investigation and has been considered as a possible treatment in seriously ill patients. There are no data in children under 2 years. • <30 kg 12 mg / kg / iv (dilute up to 50 ml with SF and administer in 1 hour) • ≥30 kg: 8 mg / kg / iv (dilute up to 100 ml with SF and administer in 1 hour). Exceptionally, and as long as there is evidence such as that which is being generated in adults, if there is a favorable response, a second infusion can be assessed 12 hours after the first infusion. In the only pediatric patient treated to date, a 8 mg / kg / iv despite weighing less than 30 kg.		
China			Not specified	Not specified

Chinese guidelines 7th /edition (03/03/2020) China's National Health Commission treatment guidelines 7th version	Tocilizumab is indicated in patients with extensive lung lesions and severe patients, and those with elevated IL-6 levels detected in the laboratory	The initial dose is 4-8mg/kg with the recommended dose of 400mg diluted with 0.9% normal saline to 100ml. The infusion time should be more than 1 hour. If the initial medication is not effective, one extra administration can be given after 12 hours (same dose as before). No more than two administrations should be given with the maximum single dose no more than 800mg.		

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Appendix 1: Observational studies

Table 1: Summary of studies reporting tocilizumab in COVID-19

Study title (Location)	Study design	Efficacy data	Safety data	Limitations/ Commentary
Observational studies				
Xu et al (44)	Retrospective, single arm study to assess the efficacy of tocilizumab in patients (n=21) with severe or critical COVID-19 pneumonia. Tocilizumab administered as a 400mg dose via IV infusion; n=3/21 received a second dose.	• At Day 5: 52.5% reported lymphocytes in peripheral blood returned to normal and CRP ↓ in 84.2% of patients. • The body temperature of all patients returned to normal on the Day 1 post tocilizumab and remained stable to Day 5. • N=15/21 patients ↓ O_2 therapy requirement and n=1/21 did not require O_2 therapy post tocilizumab. • CT scans showed lung lesion opacity was absorbed in 90.5%.	• No adverse reactions reported	• Single centre, non-randomised observational study with a small sample size, and no control arm • Risk of confounding due concomitant administration of other anti-viral and anti-inflammatory therapies • Based on these results, China updated its COVID-19 treatment guidelines, approving the use of tocilizumab to treat patients with severe or critical disease (45).
Luo et al (46)**.**	A retrospective, single centre, observational study to describe the efficacy of tocilizumab in patients (n=15) diagnosed moderate (n=2), serious (n=6) and critical (n=7) COVID-19.	• CRP and IL-6 ↓ and normalised in patients (n=11/12) who were alive at Day 7. • Tocilizumab in combination with methylprednisolone failed to improve disease activity in critically ill patients.	• Safety data not reported	• Single centre, non-randomised observational study with a small sample size, and no control arm. • Timing of baseline laboratory assessments were not reported. • Methods stated that analysis of clinical outcome would be reported but no definition of clinical outcome was provided, and no analysis was presented in the results or discussion.
Alberici et al (47)	The single centre observational study reports a descriptive analysis of the outcomes of 6 kidney transplant patients diagnosed with COVID-19 who were treated with tocilizumab	• ↓ O_2 therapy requirement in n=3/6 patients • Improvement in radiological findings (n=2/6) showed amelioration of radiological findings. • N=2/6 patients treated with tocilizumab died and n=1/6 patient was discharged from hospital 9 days after the administration of	• Safety data not reported	• Single centre, non-randomised observational study with a small sample size, and no control arm. • Risk of confounding due concomitant administration of other anti-viral, immunomodulatory and anti-inflammatory therapies • Results are specific to kidney transplant patients.

		tocilizumab. N=3/6 remain as inpatients at time of publication.		
Alattar et al (48)	This single centre observational study reports a descriptive analysis of the clinical characteristics and outcomes of patients (n=25) with severe COVID-19 who were admitted to ICU and were treated with tocilizumab	• N=9/25 achieved the primary endpoint of being discharge alive from ICU by day 14. N=13/25 are alive in ICU. N=3/25 died. • % of patients on invasive ventilation ↓ from n=21/25 at the time of tocilizumab initiation to n=14/25 (60%) on day 7 (P = .031) and n=7/25 (28%) on day 14 (P = .001).	• N=23/25 reported ≥1 AE. • anaemia (n=16/25), ↑ ALT (n=11/25), and QT interval prolongation (n=5/25). • n=4/25 developed secondary bacterial respiratory tract infections (n=2/25 Klebsiella pneumoniae, n=1/25 Pseudomonas aeruginosa and n=1/25 Staphylococcus aureus). • N=1/25 reactivation of oral Herpes Simplex infection • N=8/25 had Candida species in their respiratory cultures.	• Single centre, non-randomised observational study with a small sample size, and no control arm. • Risk of confounding due concomitant administration of other anti-viral, immunomodulatory and anti-inflammatory therapies. • No baseline variables including baseline CRP, age, co-morbidities, dose of tocilizumab were found to be independently associated with the primary outcome. • The authors report that it was not possible to determine whether AEs were treatment related.
Sciascia et al (31)	A prospective open label, single-arm multicentre study on off-label use of tocilizumab in hospitalised adult patients (n=63) with severe COVID-19.	• Observed improvement in the levels of ferritin, CRP, D-dimer post treatment with tocilizumab. • Mortality at 14 days was 11% (n=7/63 patients) • D-dimer level at baseline, but not IL-6 levels were predictors of mortality. • No observed differences between the route of administration in terms of mortality. • Tocilizumab administration within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2 95%CI 1.3-6.7, p<0.05).	• No moderate-to-severe AEs attributable to tocilizumab were recorded.	• Multi centre, non-randomised observational study with a small sample size, and no control arm. • Risk of confounding due concomitant administration of other anti-viral and anti-inflammatory therapies. • The laboratory results were graphically presented and not tabulated. The timing of when the laboratory assessments were conducted was not reported. • 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. It is unclear whether these routes of administration are interchangeable and whether this has an impact on the study results.

Quartuccio et al (27)	A retrospective, single centre, observational case-control study of baseline laboratory and immunological features in patients (n=111) who were hospitalized with COVID-19 pneumonia who were treated with standard of care (SOC) or tocilizumab (8mg/kg by intravenous infusion).	• All patients in the SOC group (antivirals) had mild disease and recovered (n=69). • In the tocilizumab group (n=42), n=27/42 received tocilizumab in ICU, N=15/42 received tocilizumab on the ward. • N=9/42 patients completely recovered, and 21/42 patients showed a clear and rapid improvement. N=12/42 patients were non-responders and n=4/42 died.	• N=17/26 patients treated with tocilizumab developed bacterial superinfection in ICU. while 1 serious bacterial superinfection occurred in a patient who received ward-based tocilizumab therapy. • SOC arm (n=69) reported no bacterial complications.	• Single centre, non-randomised observational study with a small sample size. • This study reports that milder hospitalized patients treated with SOC and treatment with tocilizumab in patients with features of a cytokine storm may be more effective outside of the ICU setting in non-ventilated patients. However, outcomes in the tocilizumab arm stratified by setting were not reported. • This study has several limitations including missing laboratory baseline data in six patients and follow-up was limited from hospital admission to discharge. Measurement of viral load was not available. Two patients in the tocilizumab group received follow up doses with anakinra. There is a risk of confounding due concomitant administration of other anti-viral and anti-inflammatory therapies.

Capra et al (30)	A retrospective, single centre, observational case-control study to evaluate the efficacy of low dose tocilizumab on mortality in COVID-19.	• Tocilizumab showed greater survival rate as compared to standard of care (HR for death, 0.035; 95% confidence interval [CI], 0.004 to 0.347; p = 0.004), after adjusting for baseline clinical characteristics (age, co-morbidities and PCR baseline levels. • Note: standard of care control arm (n=23/85; hydroxychloroquine 400 mg daily and lopinavir 800 mg daily plus ritonavir 200 mg daily).	• No side effects or infections were reported in this observation.	• Single centre, non-randomised observational study with a small sample size. • Tocilizumab was administered in non-ventilated patients who may have had milder disease and therefore a better prognosis. • Follow up is incomplete as some patients remain in hospital. • The dose of intravenous tocilizumab utilised in the study was lower than the recommended posology for CAR-T related CRS. • Patients (n=27) also received subcutaneous administration of tocilizumab which is not licensed in CAR-T related CRS and may have impacted the study results. • There is also potential confounding from concomitant administration of multiple drug interventions as part of standard of care.

Toniati et al (32)	A prospective, single centre, observational case series of patients (n=100) with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support was analysed to determine whether intravenous administration of tocilizumab was associated with improved outcomes.	• At 24-72 hours post tocilizumab administration, n=58/100 showed a rapid improvement of clinical and respiratory condition. N=37/100 stabilized compared to the rapidly declining pre-tocilizumab condition, and 5 patients died. • Day 10 - the respiratory condition improved or stabilized in n=77/100 and n=15/100 were discharged. Respiratory condition worsened in 23 (23%) patients, of whom 20 died. • N=57/100 were treated outside the ICU. Post tocilizumab: n=37/57 improved and suspended NIV, n=7/57 patients remained stable in NIV, and n=13/57 patients worsened (10 died, 3 were admitted to ICU). • N=43/100 were treated in ICU. N=32/43 improved (17 of them were taken off the ventilator and were discharged to the ward), n=143 remained stable and n=10/47 died.	• N=3/100 cases of severe AEs • N=1/100 had gastrointestinal perforation which required surgery.	• Single centre, non-randomised observational study with a small sample size, and no control arm. • The authors report that D-Dimer levels remained high, suggesting that tocilizumab was able to act only partially on the inflammatory cascade and might have had a minimal or no effect on down-modulating active coagulation. • The ERG highlights that there is also potential confounding of multiple antibacterial, antiviral and anti-inflammatory interventions as part of standard of care.
Colaneri et al (37)	A retrospective analysis of critically ill patients treated with tocilizumab (n=21) matched using propensity score to patients treated with SOC (n=21, a combination of hydroxychloroquine, azithromycin and prophylactic dose of low molecular weight heparin) was conducted in patients with COVID-19 pneumonia who were prospectively enrolled in SMAtteo COvid19 REgistry (SMACORE).	• Tocilizumab did not significantly affect risk of ICU admission (OR 0.11; 95% CI 0.00 - 3.38; p = 0.22) or 7-day mortality rate (OR 0.78; 95% CI 0.06 - 9.34; p = 0.84) when compared with SOC.	• No AE was detected following tocilizumab administration	• The results of this study suggest that tocilizumab did not affect the ICU 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 of absence of treatment effect. • The clinical endpoint of 7-day mortality may be insufficient to assess the mortality outcome in COVID-19. • Propensity score matching can reduce the bias since it mimics randomization. However, 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.
Roumier et al (49)**.**	A retrospective analysis of selected COVID-19 patients (n=30) with severe pneumonia, who were treated with intravenous tocilizumab. A comparison with a control group of patients (matched for age, gender and disease severity was performed to compare patient outcomes with patients who received tocilizumab versus SOC.	• Tocilizumab reduced the requirement of subsequent mechanical ventilation when compared against SOC (weighted OR: 0.42; 95%CI 0,20-0,89, p=0,025) while an unadjusted analysis showed a trend towards a reduction of mortality (OR: 0.25 95%CI [0.05-0.95], p=0.04). • Tocilizumab significantly reduced the risk of subsequent ICU admission when compared against SOC (weighted OR: 0.17; 95%CI [0.06-0.48]; p=0,001).	• No safety data was reported.	• Single centre, non-randomised observational study with a small sample size. • The report provided summary results only; however, they did not present sufficient information in the study to enable the ERG to conduct an assessment of the methodology employed and the results. • This is a pre-print publication which has not been peer-reviewed and should not be extrapolated as an indication of confirmed treatment effect.
Rimland et al (35) ***Note: this study is a pre-print and has not been peer-reviewed.***	A retrospective observational study of patients (n=11) with COVID-19 who were treated with tocilizumab all of whom required advanced ICU care and nine (82%) of whom were critically ill requiring mechanical ventilation in ICU at the time of tocilizumab administration	• Inflammatory markers (CRP and fibrinogen) ↓ post tocilizumab and at Day 5. However, other laboratory markers did not show clear trends towards improvement. • No clinical improvement in temperature or O_2 oxygen requirements in most patients following treatment with tocilizumab. • At end of follow-up, patients had been observed for a median of 17 days (IQR=11-24) post tocilizumab; n=3/11 died; n=5/11 remained in critical condition in ICU the intensive care unit (ICU), N=1/11 transferred from ICU to the ward and n=2/11 were discharged.	• N=2/11 were diagnosed with ileus and n=2/11 two were diagnosed with bacterial pneumonia after tocilizumab administration • No other serious AEs were observed.	• Single centre, non-randomised observational study with a small sample size. • The authors suggest that tocilizumab was administered too late in the disease process to offer benefit and suggest that tocilizumab should be used with caution in severe and critically ill patients.
Wadud et al (33)	A retrospective case control study in COVID 19 positive patients with ARDS who required mechanical ventilation (n=94), to determine	• Tocilizumab was associated with a longer length of stay (average 17.9 days) than in the SOC group (LoS was not reported).	• No safety data was reported.	• A small single centre, retrospective analysis. • The authors suggested that there is a mortality benefit associated with tocilizumab. However, mortality is affected by multiple, confounding factors which were not discussed in the analysis. The time frame in which mortality

	whether clinical outcomes in terms of mortality and length of stay was lower in patients who received tocilizumab (n=44) than in the control arm (n=50).	• The survival rate was lower in the control group (48%) relative to 61.36 % in patients who received tocilizumab.		would be measured was not reported which limits our ability to assess the results. • The report fails to define what constituted SOC in the control arm and whether patients in the tocilizumab group received SOC which limits our ability to assess the results.
Marfella et al (38) ***Note: this study is a pre-print and has not been peer-reviewed.***	A retrospective, observational analysis to evaluate the effects of tocilizumab therapy on outcomes of hyperglycaemic (n=31) and normoglycemic (n=47) Covid-19 patients with pneumonia.	• Hyperglycaemic patients had IL-6 levels at admission 5-fold higher as compared to the normoglycemic patients. The elevated IL-6 levels were persisted in patients with hyperglycaemia even after tocilizumab administration. • In a risk adjusted Cox-regression analysis, tocilizumab in hyperglycaemic patients did not attenuate the risks of severe outcome (mechanical ventilation and/or death) as demonstrated in normoglycemic patients (p<0.009).	• No safety data was reported.	• Hyperglycaemia has been shown to increase IL-6 and IL-6R which has been suggested as a severity predictor in Covid-19. The authors suggest that the reduced effects of tocilizumab in hyperglycaemic patients may due to the higher baseline and persistent plasma IL-6 levels. • This is a small, single centre, non-randomised observational study which has not been peer reviewed.
Ramaswamy et al (36)	A retrospective, observational, case control study to evaluate the impact tocilizumab has on short-term survival in patients with severe COVID-19 infection.	• Tocilizumab was associated with a 75% reduction in the risk of inpatient death when compared with standard of care (HR 0.25; 95% CI 0.07-0.90) in the adjusted Cox proportional hazards model. • The treatment effects model found a 52.7% reduced risk of dying associated with patients treated with tocilizumab compared to standard of care (RR 0.472; 95% CI 0.449-0.497).	• No safety data was reported.	• The analysis suggests that tocilizumab may offer short-term survival benefit in patients with severe COVID-19 disease. • This study is a pre-print and has not been peer-reviewed. The ERG highlights the non-randomised nature of the study, the sample size and the risk of selection bias in this case-control studies.
Kimmig et al (42) ***Note: this study is a pre-print***	A retrospective, observational analysis of patients (n=60) with COVID-19 pneumonia who were admitted to ICU to	• No efficacy data was reported.	• Tocilizumab was associated with a higher incidence of secondary bacterial infections including hospital acquired pneumonia and	• The authors report that cases were randomly selected but do not provide further information regarding how cases were considered for inclusion in the study.

and has not been peer-reviewed.	determine whether there was an association between tocilizumab administration and secondary infections.		ventilator associated pneumonia (64.3% vs. 31.3% p=0.010).	• The study does not specify whether patients received other concomitant medicines e.g. glucocorticoids which could have confounded the results. • Owing to the lack of randomised nature of the study it is plausible that patients receiving tocilizumab were sicker, had a worse prognosis and therefore more likely to acquire a secondary infection.
Sánchez-Montalvá et al (50) ***Note: this study is a pre-print and has not been peer-reviewed.***	A retrospective, observational analysis of patients (n=60) with COVID-19 who were hospitalized in non-ICU wards and received treatment with tocilizumab. administration.	• The authors report a 7-day mortality of 26.8% (n=22/60) in patients treated with tocilizumab.	There were no adverse events attributed to tocilizumab	• Limitations of this study include its retrospective nature, lack of a control arm and potential confounding from concomitant administration of multiple anti-viral agents. • The authors report that the mortality rate associated with tocilizumab in this study is higher than experience with remdesivir and similar to the mortality of 22.1% reported in another study with lopinavir/ritonavir. However, the ERG highlights that at day 7 follow up 41.5% (n=34/60) were discharged and 28.1% (n=23/60) were still in hospital on a ward or in ICU and had no final outcome i.e. discharge or death.

Appendix 2: Clinical Trial Registers:

A search of the following clinical trial registers www.clinicaltrials.gov, Chinese clinical trial registry (www.Chictr.org.cn). The search highlighted that there are 39 clinical trials ongoing to assess the efficacy and safety of tocilizumab in COVID-19.

1. Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS). A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19 (NCT04306705).
    - Primary outcome: Proportion of participants with normalization of fever and oxygen saturation through Day 14.
2. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (NCT04317092). This is a multicentre, single-arm, open-label, phase 2 study.
    - Primary outcome: One-month mortality rate
3. Tocilizumab for SARS-CoV2 (COVID-19) Severe Pneumonitis. Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 Infection with Severe Multifocal Interstitial Pneumonia. An open label single group assignment study. (NCT04315480).
    - Primary outcome: arrest in deterioration of pulmonary function and improving lung function at 7 days.
4. A single arm open label study to assess tocilizumab in the prevention of Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE). Early Institution of Tocilizumab Titration in Non-Critical Hospitalized COVID-19 Pneumonitis (NCT04331795)
    - Primary outcome measures: Clinical response, and biochemical response
5. Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID). Pilot, Randomized, Multicentre, Open-label Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of SARS-CoV-2 Infection (COVID-19). NCT04332094.
    - Primary outcome measures: In-hospital mortality, and need for mechanical ventilation in the ICU
6. Tocilizumab in the Treatment of Coronavirus Induced Disease (COVID-19) (CORON-ACT). A multicentre, double-blind, randomized controlled phase II trial. NCT04335071
    - Primary outcomes: Number of patients admitted to ICU, number of patients intubated, number of deaths,
7. A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia (COVACTA). A Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia NCT04320615.
    - Primary endpoint: Clinical Status Assessed Using a 7-Category Ordinal Scale at day 28.
8. Efficacy and Safety of Tocilizumab in the Treatment of SARS-Cov-2 Related Pneumonia (TOSCA) a Proof of Concept Study - NCT04332913.
    - Primary endpoint: Percentage of patients with complete recovery defined as fever disappearance and return to normal peripheral oxygen saturation values (SpO2) after 14 days from the end of treatment with tocilizumab

9. Checkpoint Blockade in COVID-19 Pandemic (COPERNICO). NCT04335305
    - Primary outcome: Percentage of patients with normalization of oxygen saturation by pulse oximetry (SpO2) ≥96% at day 14.
10. Prospective Study in Patients with Advanced or Metastatic Cancer and SARS-CoV-2 (COVID-19) Infection (IMMUNONCOVID). Prospective, Controlled, Randomized, Multicentre Study to Compare the Efficacy of a Chloroquine Analog (GNS561), an Anti PD-1 (Nivolumab) and an Anti-interleukine-6 Receptor (Tocilizumab) vs Standard of Care in Patients With Advanced or Metastatic Cancer and SARS-CoV-2 (COVID-19) Infection NCT04333914.
    - Primary outcome: 28-day survival rate
11. Personalised Immunotherapy for SARS-CoV-2 (COVID-19) Associated with Organ Dysfunction (ESCAPE). NCT04339712
    - Primary outcome: Change of baseline total sequential organ failure assessment (SOFA) score, Improvement of lung involvement measurements and Increase of pO2/FiO2 ratio at day 8
12. Treatment of COVID-19 Patients with Anti-interleukin Drugs (COV-AID). A Prospective, Randomized, Factorial Design, Interventional Study to Compare the Safety and Efficacy of Combinations of Blockade of Interleukin-6 Pathway and Interleukin-1 Pathway to Best Standard of Care in Improving Oxygenation and Short- and Long-term Outcome of COVID-19 Patients With Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome NCT04330638.
    - Primary endpoint: time to clinical improvement at day 15.
13. Anti-il6 Treatment of Serious COVID-19 Disease with Threatening Respiratory Failure (TOCIVID). An Open-Label, Multicentre Sequential and Cluster Randomized Trial NCT04322773.
    - Primary outcome: Time to independence from supplementary oxygen therapy (days from enrolment to 28 days)
14. CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) (CORIMUNO-TOC). Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patient NCT04331808
    - Primary outcomes: WHO progression scale at day 7 and 14, survival at day 14, 28 and 90 days, 28 day ventilator free days, respiratory acidosis at day 4, PaO2/FiO2 ratio from day 1 to 14, time to oxygen supply independency at 14 days, duration of hospitalisation to 90 days, time to negative viral excretion to 90 days, time to ICU discharge to 90 days, time to hospital discharge to 90 days.
15. Multi-centre, randomized, controlled clinical trial study of fapiravir tablets combined with tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). ChiCTR2000030894
    - Outcomes being assessed: clinical cure rate, viral conversion rate from positive to negative, duration of fever, lung imaging improvement time, rate of non-invasive and invasive mechanical ventilation, mean length of stay, CPR, lymphocyte count (absolute and %).
16. Multicentre, randomized controlled clinical study of the efficacy and safety of tocilizumab in new coronavirus pneumonia (COVID-19). ChiCTR2000029765
    - Outcomes being assessed: cure rate, mortality, ventilator utilisation, length of stay
17. Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalised COVID-19 Patients with High Risk of Progression. An Open-label, Randomized,

Cross-over Interventional Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalised COVID-19 Patients with High Risk of Progression. NCT04345445.

- Primary endpoint: The proportion of patients requiring mechanical ventilation and Mean days of ventilation

18. Tocilizumab for Prevention of Respiratory Failure in Patients with Severe COVID-19 Infection. A Phase II Study of IL-6 Receptor Antagonist Tocilizumab to Prevent Respiratory Failure and Death in Patients with Severe COVID-19 Infection. NCT04377659
    - Primary endpoint: Progression of respiratory failure or death
19. Efficacy of Early Administration of Tocilizumab in COVID-19 Patients. An Open-label Randomized Multicentre Study to Evaluate the Efficacy of Early Administration of Tocilizumab (TCZ) in Patients With COVID-19 Pneumonia. NCT04346355
    - Primary endpoint: Entry into Intensive Care with invasive mechanical ventilation or death from any cause or clinical aggravation
20. Serum IL-6 and Soluble IL-6 Receptor in Severe COVID-19 Pneumonia Treated with Tocilizumab (UHID-COVID19). Prognostic Value of Serum Interleukin-6 (IL-6) and Soluble Interleukin-6 Receptor (sIL-6R) in Severe Coronavirus Disease (COVID-19) Pneumonia Treated with Tocilizumab - a Prospective Single Centre Study (UHID-COVID19). NCT04359667.
    - Primary endpoint: serum interleukin-6 and soluble interleukin-6 receptor as biomarkers of clinical outcomes in patients with severe coronavirus disease (COVID-19) pneumonia treated with tocilizumab
21. The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation. NCT04377750
    - Primary endpoint: One-month mortality rate.
22. A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia. A Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. NCT04372186
    - Primary endpoint: Cumulative Proportion of Participants Requiring Mechanical Ventilation by Day 28
23. Efficacy of Tocilizumab on Patients With COVID-19. Prospective, single-centre, placebo-controlled, blinded, randomized controlled trial at MGH. NCT04356937
    - Primary outcome: Proportion of patients that require mechanical ventilation at day 28.
24. A Study to Investigate Intravenous Tocilizumab in Participants With Moderate to Severe COVID-19 Pneumonia (MARIPOSA). A Phase-II, Open-Label, Randomized, Multicenter Study to Investigate the Pharmacodynamics, Pharmacokinetics, Safety, and Efficacy of 8 mg/kg or 4mg/kg Intravenous Tocilizumab in Patients With Moderate to Severe COVID-19 Pneumonia NCT04363736
    - A Primary endpoint: Concentration of C-Reactive Protein (CRP) at day 7.
25. Tocilizumab Treatment in Patients With COVID-19. Phase II, single-arm, open-label, prospective, blinded, clinical trial with Tocilizumab as the sole agent. NCT04363853
    - A Primary endpoint: blood chemistry, hematic biometry, blood gas, and thorax radiography at 25 hours, 48 hours and 7 and 14 days.

26. Tocilizumab Versus Methylprednisolone in the Cytokine Release Syndrome of Patients With COVID-19. Prospective randomized controlled phase 2 study NCT04377503
    - A Primary endpoint: Patient clinical status 15 days after randomization
27. Assessment of Efficacy and Safety of Tocilizumab Compared to DefeROxamine, Associated with Standards Treatments in COVID-19 (+) Patients Hospitalized In Intensive Care in Tunisia (TRONCHER). Multicentric, Comparative, Randomized Study. NCT04361032
    - A Primary endpoint: 90 day mortality rate.
28. Tocilizumab for Patients with Cancer and COVID-19 Disease NCT04370834
    - A Primary endpoint: To provide observations on clinical outcomes associated with tocilizumab administration in cancer patients with severe acute respiratory syndrome (SARS) coronavirus 2 (COVID-19) disease.
    - Primary endpoint: frequency of response, length of time from level of care to step down level of care, survival up to 1 week.
29. Checkpoint Blockade in COVID-19 Pandemic (COPERNICO). A prospective, multicenter, randomized, controlled, open-label, phase 2 clinical trial NCT04335305
    - Primary endpoint: Percentage of patients with normalization of oxygen saturation by pulse oximetry (SpO2) ≥96% at day 14
30. Favipiravir Combined with Tocilizumab in the Treatment of Corona Virus Disease 2019. A Multicenter, Randomized and Controlled Clinical Trial Study NCT04310228.
    - Primary outcome: clinical cure rate at 3 months.
31. Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-19 (SARS-CoV-2 Infection). An Open-Labelled, Randomized Phase 3 Trial NCT04361552
    - Primary outcomes: 7-day length of invasive mechanical ventilation (MV) and 30 day mortality rate.
32. Randomized Evaluation of COVID-19 Therapy (RECOVERY). A randomised, parallel assignment open label trial to evaluate COVID-19 therapy. NCT04381936
    - Primary outcome: all cause mortality within 28 days of randomisation.
33. Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19. A non-randomised, open-label, multi-centre prospective study. NCT04380818
    - Primary outcome: Efficacy of low-dose pulmonary irradiation assessed by change in PAFI O2 by 20% from day 2 after radiotherapy.
34. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP). Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia NCT02735707
    - Primary outcomes: all cause mortality (90 days), days alive and outside of ICU (to day 21)
35. The Fleming [FMTVDM] Directed CoVid-19 Treatment Protocol (FMTVDM). A randomised, factorial assignment trial. NCT04349410
    - Primary outcome: Improvement in FMTVDM Measurement with nuclear imaging
36. Plasma Exchange in Patients With COVID-19 Disease and Invasive Mechanical Ventilation: a Randomized Controlled Trial (REP-COVID). A multicentre open label randomized controlled clinical trial. Note tocilizumab is one of the listed comparators in the experimental arm. NCT04374539.
    - Primary outcome: Impact of plasma exchange on mortality at 28 days.

37. An Open Randomized Study of Dalargin Effectiveness in Patients with Severe and Critical Manifestations of SARS-COVID-19. An Open Randomized Study of the Effectiveness of the Drug Dalargin for the Prevention and Treatment of Symptoms of Pulmonary Complications in Patients with Coronavirus Infection (SARS-COVID-19). An Open Randomized Study Note tocilizumab is one of the listed comparators in the experimental arm. NCT04346693
    - Primary outcomes: The change of viral load in patients with SARS-COVID-19 (baseline and day 10), The frequency of development of Acute Respiratory Distress Syndrome (ADRS) (through study completion), the frequency of early mortality (up to 30 days), the frequency of late mortality (up to 90 days), clinical status at the time of completion of participation in the study.
38. Ultra-Low Doses of Therapy with Radiation Applicated to COVID-19 (ULTRA-COVID). Note tocilizumab is one of the listed comparators in the experimental arm. NCT04394182
    - Primary outcomes: oxygen therapy status at day 2, oxygen saturation at day 2.
39. Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care (POPS) (POPS or POP02). A prospective observational study. Note tocilizumab is listed as one of the treatments under evaluation. NCT04278404
    - Primary outcome measures: Clearance, volume of distribution, elimination rate constant, half-life, absorption rate constant, area under the curve, maximum concentration, time to achieve maximum concentration.

Appendix 3: H Score

The H score generates a probability for the presence of secondary haemophagocytic lymphohistiocytosis (sHLH). HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator which is available at http://saintantoine.aphp.fr/score/

HScore for secondary HLH, by clinical parameter

Clinical Parameter	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1.5 mmol/L	0
1-5 – 4.0 mmol/L	44
≥4.0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000-6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
< 30 IU/L	0
≥ 30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

*defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110000 platelets per mm³ or less, or all of these criteria combined

†HIV positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

The table above is from publication by Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet [Internet]. 2020 Mar [cited 2020 Mar 17];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext

Appendix 4: 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
- Randomized 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	Results	Studies of relevance relating to studies reporting tocilizumab in COVID-19
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))	198	26
LitCovid	"Tocilizumab" OR "Interleukin-6" or "IL-6"	82	20
MedRxiv	"Tocilizumab" OR "Interleukin-6" or "IL-6"	90	6
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) AND “Tocilizumab”	37	37
Chictr.org.cn	“Tocilizumab” from November 2019	2	2