Rapid Evidence Review

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

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National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

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Key changes (highlighted in yellow) between version 3 (20th of May 2020) and version 4 (21st of August 2020): Updated evidence (n=8 publications) relating to tocilizumab in COVID-19 added. Only RCTs and published prospective and retrospective studies with ≥100 patients treated with tocilizumab in COVID-19 have been included in the evidence review update. Guidelines which have been updated as of 1st of July 2020 are only included in the version 4 review. An overview of the limitations of observational study results has been provided in light of the large amount of observational evidence in this area.

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 observational 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 and suggested 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. Unpublished interim results from the COVACTA trial which is the first randomised, double-blind, placebo-controlled phase III RCT in severe COVID-19 associated pneumonia did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality at 28 days. A multicentre, open label, phase II RCT in Italy also reported no differences in ICU admissions and mortality in patients with COVID-19 when treated with tocilizumab compared with standard of care (1). The RECOVERY study is ongoing and is evaluating tocilizumab in patients with clinical evidence of a hyperinflammatory state and progressive COVID-19, with results expected in the coming weeks. Overall, observational studies published to date have suggested that tocilizumab may be a promising candidate to improve the outcomes of patients with severe or critical COVID-19 infections. However, the body of evidence published to date are predominantly single centre, non-randomised studies with small sample sizes of sub-optimal methodological quality which are prone to various biases and structural limitations. The therapeutic benefit suggested in observational studies has not yet been replicated in randomised controlled trials. Adequately powered, prospective and well-designed, comparative randomised controlled trials are critical sources of evidence of effectiveness and are key to underpin optimal evidence-informed decision-making and guidance in COVID-19.

Conclusion

Our Rapid Review finds that the emerging RCT evidence[1] for tocilizumab has not demonstrated a significant difference in outcomes measured versus standard of care. An increase in side effects was observed in the tocilizumab arm over standard of care. Further studies including the RECOVERY trial and the full publication of the COVACTA trial are awaited.

[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-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(2). Interleukin-6 (IL-6) is a key pro-inflammatory cytokine that is elevated in CRS. Suppression of proinflammatory IL-1 family members and IL-6 are likely to have a therapeutic effect in many inflammatory diseases, including viral infections (3). 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 (4,5). Tocilizumab prevents IL-6 from binding to soluble and cell associated IL-6 receptors inhibiting IL-6-mediated signalling (6).

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 (7–10). Clinical data suggests that disease progression in COVID-19 infected patients may be driven by a dysregulated immune response resulting in a cytokine storm (11). 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 (12). 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 (13). 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 (14–20). Tocilizumab has shown efficacy for other iatrogenic causes of CRS and is licensed for the treatment of CAR-T cell-associated CRS (13). 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 (21).

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 (22). The identification of a unique definition of CRS during COVID-19 infection is crucial to better customize the management of critical patients (23). 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 the 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 (11). 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 anti-viral and anti-microbial immunity, which could result in delayed virus clearance and perpetuate the COVID-19 illness and potentially promote secondary bacterial infection (24).

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

In total, 167 studies have been identified from our search strategy including observational studies (n=74) and case series/reports (n=93). A rapid critical appraisal of the phase 3 trial study results (n=1), phase II trial results (n=2) as well as published prospective and retrospective studies (n=5) with n ≥100 patients treated with tocilizumab in COVID-19 was conducted by the ERG and are summarised in the following text and in Appendix 1.

Interim results of the first phase III RCT in severe COVID-19 associated pneumonia were reported on July 29th, 2020. COVACTA is a randomized, double-blind, placebo-controlled, phase III study of tocilizumab in hospitalized adult patients with severe COVID-19 associated pneumonia. In total 450 patients were randomized to receive tocilizumab 8 mg/kg IV (maximum dose of 800 mg) or placebo along with current standard of 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 difference in mortality, mechanical ventilation, time to hospital discharge and additional ICU variables at Week 4. An interim analysis was conducted, and the results announced via press release on July 29th, 2020 stating that the trial had failed to reach its primary or secondary endpoints. The odds ratio for clinical 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. At Week 4, rates of infections and serious infections were 38.3% and 21.0% in the tocilizumab arm and 40.6% and 25.9% in the placebo arm, respectively. The COVACTA study did not identify any new safety signals for tocilizumab. Although the results were announced in a press release the results of this study are not yet available but are being submitted for publication in a peer reviewed journal (25). The RECOVERY trial is not expected to terminate early as patients recruited to the study differ from those recruited to the COVACTA study. The RECOVERY trial considers the efficacy of tocilizumab in patients with severe COVID-19 whose disease has progressed with evidence of hyperinflammation while the COVACTA study did not consider evidence of hyperinflammation in the inclusion criteria (25,26).

In June 2019, a press release from the Italian Medicines Agency (AIFA) reported results from an interim analysis of a randomized, multicentre, open-label phase II study to assess the efficacy of tocilizumab compared with standard of care in patients with COVID-19 pneumonia (n=126). No significant differences were observed in the total number of admissions to ICU (10.0% vs 7.9%) or 30-day mortality (3.3% vs 3.2%) between tocilizumab and standard of care. 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. These results have not been published and have not been peer-reviewed (1). In contrast, results from the TOCIVID-19 study (pre-print) which is a multicentre, single-arm, open-label, phase II study suggest that tocilizumab may offer a mortality benefit in patients with COVID-19. The authors suggest that the results should be hypothesis-generating given the significant limitations associated with this study including missing data and study design (27). A press release from the Paris University Hospital Trust (AP-HP) 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 (28). Results of this study are not yet available but are being submitted for publication in a peer-reviewed journal.

There are limited robust 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 (29–32). 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 (31,33–36). 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, the dose and timing of administration of tocilizumab was variable and clinical decisions regarding a patient's eligible for intubation were decided by the hospital's committee which may have biased the survival rates reported in the study (37). 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) (38). 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 (30). 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. 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 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 (39). Colaneri *et al* report an analysis of critically ill patients with COVID-19 pneumonia who were prospectively enrolled in 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 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 (40). 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 (41). 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 (42). Several case reports/series of interest report the experience of tocilizumab in renal transplant and liver transplant patients (43,44). However, these are single case observations and cannot be extrapolated as an indication or absence of treatment effect.

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 sub-optimal 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, 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.

Timing and route of administration of tocilizumab

The timing of administration in relation to disease course remains uncertain and 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 (6). 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 (45,46).

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 (30,47). Other studies have suggested that treatment with tocilizumab might favour the persistence of the SARS-CoV-2 virus and iatrogenic infections (33). 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 (48). 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 (31,49). The RCT evidence from COVACTA indicated an increase in infections in the tocilizumab arm over standard of care. 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.

Treatment guidelines

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

Guideline (Date published, version). Group	Recommendation	Dosing, frequency and duration
USA National Institute of Health. Last updated 30/07/2020 (50)	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
Belgium Belgian Task Force Group Version 12 updated: 18/07/2020 (51)	Any use should be limited to clinical trials or within Belgian/international cohort studies if possible.	Not specified
Spain (52) Ministry of Health Spain: COVID-19Technical Documents for Healthcare Professionals – medical treatment. Updated 09/07/2020	The AEMPS recommends following the hospital's clinical management protocols and that -to the extent possible- treatment with this drug be advanced to those phases of the disease in which it is more likely that stopping the inflammatory cascade has an effect on the need for ventilation.	**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. **Paediatric 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 favourable response, a second infusion can be assessed 12 hours after the first infusion. In the only paediatric patient treated to date, a 8 mg / kg / iv despite weighing less than 30 kg.

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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 (47)	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 to 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 (53)	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 (54)	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 (55)	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 (30)	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 (33)	A retrospective, single centre, observational casecontrol 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. • The authors report that n=9/42 patients treated with tocilizumab completely recovered, and n=21/42 patients showed a clear and rapid improvement. N=12/42 patients treated with tocilizumab 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 (29)	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 (31)	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 (40)	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. • 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 (35)	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 (36) ***Note: this study is a pre-print and has not been peerreviewed.***	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 (32)	A retrospective case control study in COVID-19 positive patients with ARDS who required mechanical ventilation (n=94), to determine whether clinical outcomes in terms of mortality and length of stay	• Tocilizumab was associated with a longer length of stay (average 17.9 days) than in the SOC group (LoS was not reported). The survival rate was lower in the control group (48%) relative to 61.36 % in patients who received tocilizumab.	• 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 would be measured was not reported which limits our ability to assess the results.

	was lower in patients who received tocilizumab (n=44) than in the control arm (n=50).			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 (42) ***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 persistent 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 IL6 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 (56)	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 nonrandomised nature of the study, the sample size and the risk of selection bias in this case control studies.

Kimmig et al (48) ***Note: this study is a pre-print And has not been peerreviewed.***	A retrospective, observational analysis of patients (n=60) with COVID-19 pneumonia who were admitted to ICU to determine whether there was an association between tocilizumab administration and secondary infections.	• No efficacy data was reported.	• 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).	• The authors report that cases were randomly • selected but do not provide further information regarding how cases were considered for inclusion in the study. 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 (57) ***Note: this study is a pre-print and has not been peerreviewed.***	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, small sample size and lack of a control arm. • 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.

Guaraldi et al (38)	A multicentre, retrospective, observational cohort study of patients with severe COVID-19 to assess the role of tocilizumab (n=179) in reducing the risk of invasive mechanical ventilation and death in patients with severe COVID-19 pneumonia versus standard of care treatment (n=365).	The authors report that after adjustment for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab treatment 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) when compared with standard of care.	In total, 24 (13%) of 179 patients treated with tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone (p<0·0001)	• Limitations of this study include its retrospective nature, potential confounding from concomitant administration of glucocorticoids which was higher in the severe group (35%) than 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. Risk of selection bias – clinical decisions regarding a patient's eligible for intubation were decided by the hospital's committee which likely biased the survival rates reported in the study. Patients who have a better chance of survival may have been selected for treatment with tocilizumab over patients who were not considered candidates for treatment. Patients whose clinical condition deteriorated more rapidly in the standard of care group may not have been considered eligible for treatment.
Price et al (41)	A single centre, retrospective observational study of patients with severe and non-severe COVID-19 who were treated with tocilizumab. The primary outcome was 14-day survival stratified according to disease severity at admission	Tocilizumab-treated patients with severe disease (n=59) had higher admission levels of high-sensitivity C-reactive protein (120 vs 71 mg/L; *P* < .001) and received tocilizumab sooner (2 vs 3 days; *P* < .001), but their survival was similar to that of patients treated with tocilizumab with non-severe disease (n=94) (83% vs 91%; *P* = .11)	Among tocilizumab-treated patients, there were few (6%) cases of neutropenia. No tocilizumab-treated patients experienced grade 4 hepatotoxicity, but a number of patients experienced worsening transaminases following treatment. It is not clear whether this increase is due to COVID-19 disease progression (either viral or CRS-related processes), antiviral medications, or from tocilizumab itself.	Limitations of this study include its retrospective nature, potential confounding from concomitant administration of glucocorticoids which was higher in the severe disease group (35%) than in the non-severe disease group (8.9%) which may have impacted on treatment outcomes.

Toniati et al (31)	A single centre prospective observational study of patients (n=100) with COVID-19 pneumonia and ARDS and hyperinflammatory syndrome requiring ventilatory support who were treated with tocilizumab in ICU (n=43) or a general ward (n=57).	At 24-72 hours, 58 patients demonstrated clinical and respiratory improvement, 37 were stable, and 5 deteriorated, of whom 4 died. Of the 57 patients treated on a general ward, 37 (65%) improved and suspended non-invasive ventilation (NIV) (median BCRSS: 1 [IQR 0–2]), 7 (12%) patients remained stable in NIV, and 13 (23%) patients worsened (10 died, 3 were admitted to ICU). Of the 43 patients treated in the ICU, 32 (74%) improved (17 were taken off the ventilator and were discharged to the ward), 1 (2%) remained stable (BCRSS: 5) and 10 (24%) died (all of them had BCRSS≥7 before TCZ). Overall, at 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients and 15 were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died.	Three cases of severe adverse events: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10	• The results should be considered preliminary, as they are from an uncontrolled series and a causal inference cannot be established. The generalisability of the results must also be considered in relation to different healthcare settings, particularly regarding the availability health care resources including ventilators and beds in ICU settings in this study which the authors highlighted were limited.
Sinha et al(34)	A retrospective observational study of IL6 receptor inhibitors (IL6ri) (sarilumab or tocilizumab) in patients (n=255) with stage IIB (n=149) and stage II (n=106) COVID-19	Patients treated in stage IIB had lower mortality than those treated in stage III (adjusted hazard ratio (aHR) 0.24, 95% confidence interval (CI) 0.08–0.74). Overall, 218 (85.5%) patients were discharged alive. Patients treated in stage IIB were more likely to be discharged (aHR 1.43, 95% CI 1.06–1.93) and were less likely to be intubated (aHR 0.43, 95% CI 0.24–0.79).	Of the 255 patients, 34 (13.3%) had secondary bacterial infections at 48 hours after receiving an IL6ri medication. Four (11.8%) of these patients died. Secondary infections were not associated with an increased risk of mortality (odds ratio (OR) 1.09, 95% CI 0.36–3.38) or decreased rate of discharge (OR 0.76, 95% CI 0.29–1.99).	The results should be considered preliminary, as the results are limited by the lack of a control group, the small size of the cohort, missing data, and the open-label, non-randomized use of IL6ri. The authors suggest that the results might also have been influenced by factors such as increased clinical experience towards the end of the observation period and differences in thresholds for hospitalization and discharge.

Gorgolas et al (37) ***Note: this study is a pre-print and has not been peer-reviewed***	A retrospective observational study reporting the compassionate use of tocilizumab in severe SARS-Cov-2 pneumonia in 186 patients.	The primary endpoint (intubation or death) was significantly different in the group receiving tocilizumab when the oxygen support was high (FiO_2 >0.5 %) compare to those with FiO_2 ≤0.5% (37% vs 13%, p<0.001). The authors report that early administration of tocilizumab, when the need of oxygen support was still below FiO_2 ≤0.5%, was significantly more effective than given it in advanced stages (FiO_2 >0.5 %), achieving lower rates of intubation or death (13% vs 37% respectively, p<0·001).	Eleven (5.9%) patients experienced serious adverse events related to tocilizumab including headache (n=1), hyperkalaemia (n=1), elevated hepatic enzymes (n=5), elevated bilirubin (n=3). There were 13 reported secondary infections post-tocilizumab administration.	The results should be considered preliminary, as they are from an uncontrolled series and a causal inference cannot be established. The authors report that the clinical status of patients and the timing of drug administration after the onset of COVID-19 symptoms were variable. There is also a risk of potential confounding from concomitant administration of glucocorticoids which may have impacted on treatment outcomes. The authors report that survival rates would also have been influenced by the UCI committee decision whether a patient was eligible for intubation or not.

Appendix 2: Clinical Trial Registers:

A search of the following clinical trial registers www.clinicaltrials.gov. The search highlighted that there are 66 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 COVID19 (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). Status: recruiting.
    - 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. Status: recruiting.
    - 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). Status: Active, not recruiting.
    - 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). Status: completed.
    - 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. Status: recruiting
    - 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 COVID19 Pneumonia NCT04320615. Status: completed.
    - 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. Status: recruiting.

- 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. Status: recruiting.
    - 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 (COVID19) 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. Status: suspended.
    - Primary outcome: 28-day survival rate
11. Personalised Immunotherapy for SARS-CoV-2 (COVID-19) Associated with Organ Dysfunction (ESCAPE). NCT04339712. Status: recruiting.
    - 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 COVID19 Patients With Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome NCT04330638. Status: recruiting.
    - 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. Status: recruiting.
    - 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. Status: active, not recruiting.
    - 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. Status: not yet recruiting.
    - 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.
    Status: recruiting
    - 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. Status: terminated.
    - 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. Status: not yet recruiting.
    - Primary endpoint: serum interleukin-6 and soluble interleukin-6 receptor as biomarkers of clinical outcomes in patients with severe coronavirus disease (COVID19) pneumonia treated with tocilizumab
21. The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation. NCT04377750. Status: recruiting.
    - 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-Pneumonia. NCT04372186. Status: active, not recruiting.
    - 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. Status: active, not recruiting.

- 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. Status: active, not recruiting.
    - 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. Status: recruiting.
    - 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. Status: not yet recruiting.
    - 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. Status: not yet recruiting.
    - A Primary endpoint: 90-day mortality rate.
28. Tocilizumab for Patients with Cancer and COVID-19 Disease NCT04370834. Status: suspended.
    - 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. Status: recruiting.
    - 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. Status: recruiting.
    - Primary outcome: clinical cure rate at 3 months.
31. Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-(SARS-CoV-2 Infection). An Open-Labelled, Randomized Phase 3 Trial NCT04361552. Status: withdrawn.
    - 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. Status: recruiting.
    - 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. Status: recruiting

- 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. Status: recruiting.
    - 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. Status: enrolling by invitation.
    - 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. Status: recruiting
    - 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. Active not recruiting
    - 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. Status: recruiting.
    - 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. Status: recruiting
    - 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.
40. Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia. NCT04445272. Status: recruiting.
    - Primary outcome: To calculate the time of intubation [Time Frame: through study completion, and average of 1 month]. To calculate the time with oxygen therapy [Time Frame: through study completion, and average of 1 month]. To calculate the

time with Non-invasive mechanical ventilation [Time Frame: through study completion, and average of 1 month]. To evaluate mortality rate [Time Frame: through study completion, and average of 1 month]

41. Low-dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19. NCT04479358. Status: not yet recruiting.
    - Primary outcome: Time to Recovery [Time Frame: 28 days]
42. A RCT - Safety & Efficacy of Tocilizumab - Tx of Severe COVID-19: ARCHITECTS. NCT04435717 Status: recruiting.
    - Primary outcome: Change in IL-12 values in the 3 study groups from the start of treatment (D0) and on days D + 1 and D + 3. [Time Frame: Day1 and Day3.].
43. Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01). NCT04435717. Status: recruiting.
    - Primary outcome: Clinical status (on a 7-point ordinal scale) at day 28 [Time Frame: up to day 28]
44. A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared with Remdesivir Plus Placebo in Hospitalized Participants with Severe COVID-19 Pneumonia. NCT04409262. Status: recruiting.
    - Primary outcome: Clinical Status as Assessed by the Investigator Using a 7-Category Ordinal Scale of Clinical Status on Day 28 [Time Frame: Day 28]
45. A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation, to Compare Standard-of-care With Anakinra and Tocilizumab Treatment the Immunomodulation-CoV Assessment (ImmCoVA) Study. NCT04412291Status: recruiting.
    - Primary outcome: Time to recovery [Time Frame: Day 1 through Day 29].
46. A Trial Using ANAKINRA, TOCILIZUMAB Alone or in Association with RUXOLITINIB in Severe Stage 2b and 3 of COVID19-associated Disease. NCT04424056. Status: not yet recruiting.
    - Primary outcome: Ventilation free days at D28 [Time Frame: 28 days].
47. Safety and Efficacy of Tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers (TOCIBRAS). NCT04403685. Status: recruiting.
    - Primary outcome: Evaluation of clinical status [Time Frame: Day 15 of the trial].
48. Tocilizumab Versus Dexamethasone in Severe Covid19 Cases. NCT04519385. Status: completed.
    - Primary outcome: survival [Time Frame: 14 days]
49. Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients with Covid-19. NCT04476979. Status: recruiting
    - Primary outcome: Survival without needs of ventilator utilization at day 14 [Time Frame: day 14].
50. Tocilizumab in Coronavirus-19 Positive Patients. NCT04423042. Status: not yet recruiting.
    - Primary outcome: All-cause mortality [Time Frame: Assessed at 30 days post treatment]
51. Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan. NCT04492501 Status: completed
    - Primary outcome: survival [Time Frame: 28 days]

52. Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 With Standard Therapy in Patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection (COVID-19). NCT04380519. Status: recruiting
    - Primary outcome: Proportion of patients, responded to the study therapy, in each of the treatment groups [Time Frame: Day 15].
53. Convalescent Plasma Treatment in COVID-19. NCT04476888. Status: recruiting.
    - Primary outcome: Decrease length of stay [Time Frame: From date on which intervention given until the date of discharge from hospital or date of death from any cause, whichever came first, assessed up to 1 month]. Overall mortality [Time Frame: From date on which intervention given until the date of discharge from hospital or date of death from any cause, whichever came first, assessed up to 1 month]. Incidence of adverse events related to Convalescent Plasma transfusion [Time Frame: After receiving intervention (CP) till 24 hours].
54. Anti-il6 Treatment of Serious COVID-19 Disease with Threatening Respiratory Failure. NCT04322773 Status: recruiting.
    - Primary outcome: Time to independence from supplementary oxygen therapy [Time Frame: days from enrolment up 28 days]
55. Study on the Use of Sarilumab in Patients With COVID-19 Infection. NCT04386239. Status: not yet recruiting.
    - Primary outcome: Proportion of patients who show an improvement of the respiratory function [Time Frame: 6 weeks]
56. CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI). NCT04331808. Status: Active, not recruiting.
    - Primary outcome: Survival without needs of ventilator utilization at day 14. Group 1 [Time Frame: 14 days]. WHO progression scale <=5 at day 4. Group 1. [Time Frame: 4 days]. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14. Group 2. [Time Frame: 14 days]. WHO progression scale at day 4. Group 2. [Time Frame: 4 days]
57. Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia. NCT04359095. Status: not yet recruiting.
    - Primary outcome: Mortality and Number of Participants with Treatment Related Severe Adverse Events as Assessed by the NCORP Guidance for Collection of Adverse Events Related to COVID-19 Infection [Time Frame: Post-intervention at day 28]
58. Factors Associated with Clinical Outcomes in Patients Hospitalized for Covid-19 in GHT-93 Est. NCT04366206. Status: recruiting
    - Primary outcome: Composite of death and mechanical ventilation [Time Frame: At 14-days follow-up]
59. Clinical Outcome of Anti-IL6 vs Anti-IL6 Corticosteroid Combination in Patients With SARS-CoV-2 Cytokine Release Syndrome. NCT04486521 Status: recruiting.
    - Primary outcome: Ventilator-Free Days [Time Frame: Up to Day 28
60. Effect of Treatments in Patients Hospitalized for Severe COVID-19 Pneumonia: a Multicenter Cohort Study. NCT04365764. Status: recruiting.

- Primary outcome: Composite of death and mechanical ventilation [Time Frame: 14-days follow-up

61. Clinical Characteristics and Outcomes of 187 Critically Ill Patients with Coronavirus Disease 2019 (COVID-19). NCT04454372 Status: not yet recruiting.
    - Primary outcome: Outcome 30 days after ICU admission [Time Frame: 30 days after admission
62. Blood Ozonization in Patients With SARS-CoV-2 Respiratory Failure. NCT04388514. Status: recruiting.
    - Primary outcome: Time of respiratory improvement and earlier weaning from oxygen support [Time Frame: 3 days, 10 days]
63. A Systems Approach to Predict the Outcome of SARS-CoV-2 in the Population of a City; COVID-19. NCT04351503 Status: recruiting
    - Primary outcome: Identification of factors associated with (i) infection (binary, yes/no), (ii) hospitalization (binary, yes/no), (iii) requirement for ICU treatment (binary, yes/no) [Time Frame: at baseline]. Duration of hospitalisations, duration of intensive care unit stays, in hospital mortality.
64. Glucocorticoids in COVID-19 (CORTIVID). NCT04438980 Status: recruiting
    - Primary outcome: Proportion of patients developing treatment failure (death, ICU admission, need for ventilator, Decrease in SpO2 <90% (in ambient air) or PaO2 <60 mmHg (in ambient air) or PaO2FiO2 <300 mmHg, associated with radiological impairment) [Time Frame: At 14 days after randomization]
65. Hyperimmune Convalescent Plasma in Moderate and Severe COVID-19 Disease. NCT04392414 Status: recruiting
    - Primary outcome: The number and proportion of patients with the normal body temperature (≤37.2 C) at the day 1, 2, 3, 4, 5, 6, 7 after the start of therapy [Time Frame: Days 1, 2, 3, 4, 5, 6, 7]
66. Conestat Alfa in the Prevention of Severe SARS-CoV-2 Infection in Hospitalized Patients With COVID-19. NCT04414631 Status: recruiting
    - Primary outcome: Disease severity [Time Frame: on day 7]

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 mm^3 or less, or platelet count of 110000 platelets per mm^3 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/PIIS01406736(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**
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”