Agency for Health Technology Assessment and Tariff System

Department of Healthcare Services

Tocilizumab in treatment of COVID-19 – a rapid review

Analytical analysis performed by the AOTMiT

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KEY INFORMATION

- The results of COVACTA – a randomised clinical trial – suggest statistically significant differences in favour of tocilizumab (TCZ) compared to standard of care, in shortening the duration of hospital stay, duration of ICU stay and the need for an ICU transfer. The post hoc analysis demonstrated a reduction of risk of the implemented treatment failure in patients not requiring mechanical ventilation at randomisation (Rosas 2020);
- Results of the safety analysis reported in COVACTA demonstrated lack of statistically significant differences in the TCZ vs. standard of care comparison (at day 28) regarding overall adverse reactions and severe adverse reactions;
- Any interpretation of COVACTA results should take into account the identified methodological limitations, including the differences between the arms with regard to the supplementary treatment used (glucocorticoids, antiviral treatment and convalescent plasma), uncompleted observation in over 25% of patients, the adopted method of result analysis and the fact that only a pre-print paper is available;
- Results of observation studies on TCZ efficacy regarding mortality risk reduction are inconsistent – results of 3 studies (Somers 2020, Biran 2020, Gualardi 2020) of the 5 studies which report results for this outcome indicate a statistically significant differences in favour of TCZ as compared to SoC. However, the results of the identified clinical trials are characterised by high uncertainty of estimates – they involve small patient samples, arms are not well-balanced with regard to confounding factors, follow-up duration is frequently insufficient to allow for demonstrating differences between the interventions. The differences in the baseline patient characteristics hinder drawing conclusions on the actual benefits of using TCZ.

SUMMARY

The objective of this analysis is evaluating the efficacy and safety of tocilizumab (TCZ) used in COVID-19 patients.

The document collates primary and secondary studies found as part of the systematic review of medical information databases (search date: 01/09/2020) Predefined inclusion criteria for the review have been met by 6 primary studies – 1 RCT (Rosas 2020 – COVACTA), 1 non-randomised quasi-experimental study (Carvalho 2020), 1 prospective observational study (Somers 2020), 4 retrospective observational studies (Guaraldi 2020, Ip 2020, Biran 2020, Tomasiewicz 2020), as well as 2 secondary studies with a meta-analysis (Boregowa 2020, Lan 2020). Efficacy was assessed in terms of risk of mortality, of transfer to the ICU or of clinical deterioration.

COVACTA, a randomised double-blind trial demonstrated statistically significant differences in favour of tocilizumab compared to standard of care for the following outcomes:

- duration of hospital stay: 20 days vs. 28 days (HR=1.35 [95%CI: 1.02; 1.79]),
- duration of ICU stay: 9.8 days vs. 15.5 days (p=0.045),
- risk of ICU transfer: 23.6% vs 40.6% (RR=0.58 [95%CI: 0.38; 0.90]), NNT=6 [95%CI: 3; 31], p=0.01).

The post hoc analysis has demonstrated a reduction of risk in terms of failure of the implemented treatment in patients not requiring mechanical ventilation at randomisation: 29% vs 42.2% (HR=0.614 [95%CI: 0.4; 0.94]), NNT=8 [95%CI: 7; 78]).

COVACTA did not observe statistically significant differences with regard to the mortality risk and the primary outcome, i.e. change of clinical status on a 7-category ordinal scale.

Interpretation of the results should take into account the identified limitations of the study:

- a higher percentage of patients in the placebo arm who received corticosteroids (at baseline or in the course of the study) (36.1% vs. 54.9%) and antiviral treatment (29.6% vs. 35.4%);
- lack of standardised standard of care (SoC), which would apply across all study sites;
- the adopted manner of the analysis of results (mITT – an analysis of results of patients who received at least 1 TCZ infusion 438/452);
- the fact that not all study participants completed the 28-day follow-up (the study was completed by 74.4% of patients from the TCZ arm and 71.5% patients from the placebo arm);
- type of the publication – *pre-print*.

The results of 3 observational studies (of the 5 studies which report results on the aforementioned outcome) are suggestive of statistically significant differences in favour of tocilizumab compared to SoC with regard to:

- survival probability post-intubation – Somers 2020 (HR=0.50 [95%CI: 0.27, 0.90]);
- mortality at day 28 of follow-up: – Somers 2020 (18% vs. 36%, p=0.01);
- mortality reduction – Biran 2020 (49% vs. 61% (HR 0.71 [95% CI: 0.56; 0.89]), Gualardi 2020: 7% vs. 20% (p=0.0007).

The safety profile analysis suggests that the safety profiles of tocilizumab and SoC are similar (COVACTA, Carvalho 2020, Guaraldi 2020). Results of COVACTA demonstrated lack of statistically significant differences in the TCZ vs. standard of care comparison (at day 28) in terms of adverse reactions in general and serious adverse reactions.

The primary studies included in the identified meta-analyses are characterised by low methodological quality (retrospective studies covering small patient samples). It should be stressed that the clinical, methodological and statistical heterogeneity of the studies generates significant uncertainty of estimates based on cumulated results.

1. OBJECTIVE

The objective of this analysis is to assess the efficacy and safety profile of tocilizumab (TCZ) used in COVID-19 patients as compared to standard of care (assessment in terms of outcomes analysed in primary studies identified in the course of the conducted systematic review, along with an assessment of the relevance of results and the reliability level of scientific evidence).

2. METHODOLOGY

The systematic review of medical information databases was carried out – PubMed and EMBASE (databases searched for version 1.0 of the Recommendations in Covid-19 on 21/04/2020; update – 01/09/2020). In order to identify papers that have not yet been published in the above-mentioned databases, a database of pre-print publications – www.medrxiv.org – was searched with the search period limited to 01/07–04/09/2020. Resources of the Covid-19 database were also used (www.covid19.aotm.gov.pl). An appendix to this document presents the search strategy adopted in the review (tables 13 -14).

Detailed criteria for including primary and secondary studies into the review are presented in the table below.

Table 1. Criteria for including primary studies into the review on tocilizumab

	Inclusion and exclusion criteria
Population	COVID-19 patients (general population or patient subpopulation)
Intervention	Tocilizumab
Comparator	Other therapeutic treatment/conservative treatment/standard of care
Outcome	Not identified – all outcomes for efficacy and safety profile assessment defined in the study protocols
Type of studies	• Controlled experimental study or experimental single-arm study; • Observational controlled study – prospective • Observational controlled study – retrospective (over 100 patients in the test arm) • Registries covering >1000 patients; • Systematic reviews with a meta-analysis; The identified systematic reviews were verified in terms of type of included primary studies. Primary studies meeting the criteria of including into this systematic review were subjected to detailed data extraction. Systematic reviews without a meta-analysis were excluded when they included the primary studies included in this review.

Levels of scientific evidence applied in this assessment were proposed in agreement with the Steering Committee which supervises works on the Polish COVID-19 recommendations, to determine the reliability level of the obtained results (Table 3). A grading system of the clinical trial results was also used, taking into account the type of the analysed outcomes (clinical /surrogate outcome) and the extent of the effect (demonstrating statistically significant differences in favour of the test or control arm) – Table 2.

Table 2. Relevance of the primary study result

Statistically significant differences in favour of the intervention – clinical outcome
Statistically significant differences in favour of the intervention – surrogate outcome
Lack of statistically significant differences between study arms
Statistically significant differences in favour of the control arm – surrogate outcome
Statistically significant differences in favour of the control arm – clinical outcome

Table 3. Evidence level [1]

Level	Description
A	• Results of >1 correctly designed RCTs, high result reliability (representative sample, ITT, blinding, correct randomisation method), • Meta-analysis of correctly designed RCTs, • Results of ≥1 correctly designed RCT(s), supplemented by data from high quality registries;
B	• Correctly designed RCT, high result reliability (representative sample, ITT, blinding, correct randomisation method)
C	• RCT with few (≤2) methodological limitations (lack of blinding, small sample, limitations of randomisation method, modified ITT (mITT))
D	• Correctly designed non-randomised controlled trial, • Correctly designed prospective cohort study, • Correctly designed registry, • Meta-analysis of the above-mentioned primary studies.
E	• Randomised or non-randomised clinical trials with numerous (>2) methodological limitations (lack of blinding, small sample, incorrect randomisation method, no ITT), • Prospective observational studies with numerous methodological limitations, retrospective controlled studies
F	• Uncontrolled experimental studies, case series
G	• Case studies

[1]Presentation of adopted reliability levels based on the ACC/AHA approach (2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines)

3. REVIEW RESULTS

This document collates results of primary and secondary studies identified in the review of scientific publications on tocilizumab in COVID-19.

The following scientific papers on the efficacy of tocilizumab in COVID-19 were found as part of the conducted search:

- 6 primary studies:
  - 1 RCT: COVACTA (Rosas 2020),
  - 1 non-randomised quasi-experimental study: Carvalho 2020,
  - 1 prospective observational study: Somers 2020,
  - 4 retrospective observational studies: Guaraldi 2020, Ip 2020, Biran 2020, Tomasiewicz 2020,
- 2 secondary studies with a meta-analysis: Boregowa 2020, Lan 2020.

It should be noted that Tomasiewicz 2020 did not meet the predefined inclusion criteria for the review (single-arm retrospective study, sample of <100 patients), however, due to the fact that it is the only study conducted on the Polish population, a decision was made to include the results of that study in the review.

A conducted non-systematic search identified a monitoring report of EUnetHTA (Project ID: RCR 03) which assessed the efficacy and safety of tocilizumab in COVID-19 treatment.

3.1. Primary studies

Table 4 collates primary studies identified in the course of the conducted review. Descriptions of the methodology and results of the studies which meet inclusion criteria for this review are presented in the tables constituting an appendix to this paper. The study did not take into account three publications identified in the course of the search of databases conducted for version 1.0 of the Recommendations in Covid-19 (date of the search: 21/04/2020) due to their size and design – case series and case studies involving small patient samples.

Table 4. Summary of identified primary studies on the efficacy and safety profile of tocilizumab in COVID-19.

No.	Study	Test arm	Control arm	Types of analysed outcomes	Reliability level
Version 1.0. of Recommendations					
1.	**Luo 2020**	TCZ	N/A	Mortality, CRP level, IL-6 levels	**F**
2.	**Xu 2020**	TCZ	N/A	Body temperature reduction, reduction of clinical symptoms, CRP level	**F**
Update					
1.	**Rosas 2020[1] COVACTA**	TCZ + SoC 1 x 8mg/kg i.v. (max 800mg)	Placebo + SoC	Clinical condition, mortality, duration of hospital stay and ICU stay, days free from mechanical ventilation, need for an ICU transfer or for intubation	**C**
2.	**Biran 2020[2]**	TCZ + HCQ, AZM, GKS 98% of patients – 400 mg, 1% of patients – 8 mg / kg 1% of patients) – NDA	HCQ, AZM, GKS	In-hospital mortality, overall survival, overall survival adjusted for time from treatment initiation	**E**
3.	**Carvalho 2020[3]**	TCZ + SoC 2 x 400 mg i.v.	SoC	In-hospital mortality, positive bacteriological / mycological culture result, use of antibiotics, need for renal replacement therapy	**E**
4.	**Guaraldi 2020[4]**	TCZ + SoC 50.8 % of patients 2 x 8 mg/kg i.v. (12-H interval) 49.2 % of patients 2 x 162 mg subcut. (simultaneous doses)	SoC	Mechanical ventilation, mortality, mortality among mechanically ventilated patients	**E**
5.	**Ip 2020[5]**	TCZ 96% of patients – 400 mg 1% of patients – 800 mg 1 % of patients – 8 mg/kg 1 % of patients – 4 mg/kg 1 % of patients) – NDA	No TCZ	Mortality on day 30	**E**
6.	**Somers 2020[6]**	TCZ 1 x 8mg/kg i.v. (max 800mg)	SoC	Likelihood of survival post intubation, mortality, duration of hospital stay, duration of mechanical ventilation, clinical deterioration	**E**
7.	**Tomasiewicz 2020[7]**	TCZ 1 x max 800 mg (dose repeated in the event of no clinical improvement)	N/A	Clinical improvement, death, less use of oxygen support therapy (pretest-posttest) SpO_2 (pretest-posttest)	**F**

AZM – azithromycin, CSs – corticosteroids, HCQ – hydroxychloroquine, SoC – standard of care, TCZ - tocilizumab

3.1.1. Experimental randomised trials

COVACTA (Rosas 2020)

COVACTA is an international, multicentre, randomised phase III clinical trial conducted in 9 countries (Denmark, France, Spain, Netherlands, Canada, Germany, United States, Italy, United Kingdom). The objective was to assess the efficacy and safety of using tocilizumab in hospitalised patients with severe COVID-19.

452 patients were randomised into two arms (2:1 randomisation) – 294 patients to the tocilizumab (i.v.) arm and 144 patients to the control placebo arm. Standard of care was used in both arms; it varied between the study centres (antiviral treatment, low-dose steroids, convalescent plasma, supportive care).

The baseline characteristics of the population in both compared arms were similar. The average age of patients participating in the trial was 61 years; 70% of them were male.

The primary outcome was the patient's clinical condition at day 28 using a 7-category ordinal scale[2]. The assessed secondary outcomes included: mortality, assessment of clinical status at day 14 of follow-up, observation, duration of hospital stay/of ICU stay, number of ventilator-free days. Statistically significant differences in favour of tocilizumab versus placebo were reported for:

- duration of hospital stay: 20 days vs. 28 days (HR=1.35 [95%CI: 1.02; 1.79], p=0.037);
- duration of ICU stay: 9.8 days vs. 15.5 days (p=0.045);
- risk of ICU transfer: 23.6% vs 40.6% (RR=0.58 [95%CI: 0.38; 0.90]), NNT=6 [95%CI: 3; 31], p=0.01) and
- reduction of the clinical failure of the implemented treatment (defined as death, withdrawal during hospitalisation, ICU transfer or need of mechanical ventilation at day 28 of follow-up among patients not mechanically ventilated at randomisation: 29% vs. 42.2% (HR=0.614 [95%CI: 0.4; 0.94)).

COVACTA did not observe statistically significant differences with regard to the mortality risk and the primary outcome, i.e. change of clinical status on a 7-category ordinal scale.

No statistically significant differences in terms of adverse reactions in general and serious adverse reactions have been reported.

Interpretation of the results of the study should take into account the identified limitations. The uncertainty of estimates of the results stems, among others, from:

- a higher percentage of patients in the placebo arm were administered corticosteroids (at baseline or in the course of the study) (36.1% vs. 54.9%) and antiviral treatment (29.6% vs. 35.4%);
- lack of standardised standard of care (SoC) which would apply across all study sites;
- the adopted manner of results' analyses (mITT – an analysis of results of patients who received at least 1 TCZ infusion 438/452);
- the fact that not all study participants completed the 28-day follow-up (the study was completed by 74.4% of patients from the TCZ arm and 71.5% patients from the placebo arm);
- type of the publication – *pre-print*.

[2] 1=discharged or ready for discharge; 2=non–intensive care unit [ICU] hospital ward, not requiring supplemental oxygen; 3=non–ICU hospital ward, requiring supplemental oxygen; 4= ICU or non–ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5= ICU, requiring intubation and mechanical ventilation; 6=ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7=death

3.1.2. Quasi-experimental studies

Carvalho 2020

The objective of Carvalho 2020, a quasi-experimental study, was to assess the impact of tocilizumab on in-hospital mortality and other clinical parameters and biomarkers of patients with critical COVID-19 compared to the control arm. The patients who met the study inclusion criteria (n=53) were allocated into the tocilizumab and standard of care arm (n=29) or the control arm – standard of care alone (n=24).

The median age of patients was 55 years in the TCZ arm and 58.5 years in the control arm. The majority of study participants were male (62% in the TCZ arm vs. 75% in the SoC arm). The use of corticosteroids was statistically significantly more common in the TCZ arm compared to the control arm (83% vs. 37%, p=0.001), which might impact the higher percentage of patients in need of mechanical ventilation at baseline (52 vs. 29%, p=0.16)

The primary outcome of the study was in-hospital mortality – death occurred in 17% of patients in the intervention arm and 4% of patients in the control arm; the difference was not statistically significant.

The results obtained for the secondary outcomes adopted in the study, i.e. the need for renal replacement therapy, use of antibiotics and positive culture and inflammatory and oxygenation markers, were not statistically significant either.

Tocilizumab was associated with a rapid oxygenation improvement (p=0.02) and a faster decline of WBC (p=0.02) and CRP levels in patients (p=0.009).

Interpretation of the results should take into account the identified limitations:

- non-blinded study;
- no randomisation;
- small population size in the study, no statistical power which would allow for demonstrating statistically significant differences;
- the use of corticosteroids was not well-balanced between the arms (83% vs. 37%), which limits the possibility of drawing conclusions on the actual clinical benefits of tocilizumab.

3.1.3. Observational studies

Somers 2020

Somers 2020 is a prospective observational study which compared results of mechanically ventilated patients who received tocilizumab and who did not. 154 patients were included (study arm: n=78, control arm: n=76). Median follow-up was 47 days (range: 28–67 days).

Baseline characteristics differed between groups, pointing to a possibly greater burden of unfavourable prognostic factors in patients from the control arm. The average age of patients receiving TCZ was lower than the age of the patients in the control arm (55 vs. 60 years). Apart from the higher percentage of patients with chronic pulmonary disease in the control arm (28% vs. 10%, p=0.006), other co-morbidities (such as hypertension, congestive heart failure, diabetes, chronic kidney disease, sleep apnoea) were more common in the patients not treated with TCZ. Furthermore, the higher percentage of patients in the TCZ cohort in whom corticosteroids (29% vs. 20%) and prone positioning (31 vs. 16%, p=0,03) was used during hospitalisation needs to be pointed to.

The primary outcome, i.e. survival probability post-intubation, was greater by approx. 50% in the intervention arm than in the control arm (HR=0.50 [95%CI: 0.27; 0.90], p=0.02).

Administration of tocilizumab was associated with statistically significantly more frequent occurrence of superinfections (54% vs. 20%); however, that did not translate into an increased risk of death. The mortality rate in the intervention arm was statistically significantly lower in all time points described in the study: 14-day case fatality rate: 7 (9%) vs. 20 (26%) (p=0.005), 21-day case fatality rate: 11 (14%) vs. 25 (33%) (p=0.006) and 28-day case fatality rate: 14 (18%) vs. 27 (36%) (p=0.01).

Apart from the reduced fatality rates, the use of tocilizumab was associated with clinical improvement (which, after adjusted models have been used, was statistically significant). More patients were discharged from hospital before study completion in the intervention arm (54% vs. 26%, p<0.001).

Interpretation of the results should take into account the identified limitations of the study:

- differences in patient characteristics to the disadvantage of the control group (age, use of corticosteroids and prone positioning during hospitalisation, reported co-morbid conditions);
- incomplete data on laboratory results (statistical models were used);
- for patients transferred from other hospitals, it is not possible to accurately describe any possible differences in treatment from other centres which may have occurred during the initial treatment period, prior to inclusion in the study;
- tocilizumab administration was based on hospital criteria but was not fully standardised.

Guaraldi 2020

The objective of Guaraldi 2020, a retrospective study was to assess the role of tocilizumab in reducing the risk of invasive mechanical ventilation and death in patients with severe COVID-19 pneumonia who received standard of care.

All patients were treated using 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.

Tocilizumab was given either intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (i.e. 324 mg in total), when the intravenous formulation was unavailable.

Of 1351 patients admitted, 40% (544) had severe COVID-19 pneumonia. 57 of 365 (16%) patients in the standard of care group needed mechanical ventilation, compared with 33 of 179 (18%) patients treated with tocilizumab (p=0.41) – 16 of 88 (18%) patients treated intravenously and 17 of 91 (19%) patients treated subcutaneously.

Statistically significant differences in terms of number of deaths in favour of the TCZ arm compared to the control arm have been reported (7% vs. 20%, adjusted HR=0.38 [95%CI: 0.17; 0.83]).

After adjusting 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). 13% of patients treated with tocilizumab were diagnosed with new infections, versus 4% of patients treated with standard of care alone (p<0.0001).

According to authors of the study, tocilizumab treatment (regardless of whether administered intravenously or subcutaneously, can reduce the risk of mechanical ventilation or death in patients with severe COVID-19 pneumonia.

Interpretation of the results should take into account the identified limitations of the study:

- retrospective study,
- short follow-up – the authors were not able to assess long-term safety of using tocilizumab.

Ip 2020

Ip 2020 studies the impact of hydroxychloroquine and tocilizumab on the course of COVID-19 in patients treated at the ICU. In the part of the study which assessed the efficacy of tocilizumab, 134 patients were included in the study arm and 413 in the control arm.

The median age of patients was 62 years in the TCZ arm and 69 years in the control arm. The majority of study participants were male (74% in the TCZ arm vs. 62% in the SoC arm).

An exploratory analysis found a trend towards an improved survival associated with tocilizumab treatment (adjusted HR=0.76 [95% CI, 0.57–1.00]), with 30-day unadjusted mortality with and without

tocilizumab of 46% versus 56%. Secondary bacteraemia and secondary pneumonia occurred in comparable patient percentages – bacteraemia: 44 (11%) of patients in the control arm, compared to 18 (13%) in the intervention arm, pneumonia: 25 (6%) vs. 12 (9%).

Interpretation of the results should take into account the identified limitations:

- retrospective study;
- the small sample size limited the exploratory analysis of tocilizumab treatment.

Biran 2020

Biran 2020 is a multi-centre retrospective observational cohort study conducted among patients with COVID-19 placed in the intensive care unit.

Taking into account the differences of baseline patient characteristics, propensity score-matching was carried out. In view of the above, a cohort of patients untreated with tocilizumab (420 patients) was matched to the tocilizumab cohort (210 patients) in terms of variables such as age, gender, diabetes, COPD/asthma, hypertension, cancer, renal failure, obesity), oxygenation <94%, quick Sequential Organ Failure Assessment (qSOFA) score, use of GCs, CRP ≤15 mg/dL vs. >15 mg/dL, and intubation or mechanical ventilator support. The median follow-up was 22 days (IQR, 11–53).

The study reported statistically significant differences in favour of the patient cohort using tocilizumab regarding overall survival (from admission to hospital) – the fatality rate was 49% vs. 61%, median overall survival was not reached (23 days) vs. 19 days, HR=0.71, [CI 95%: 0.56; 0.89]; p=0.0027).

In terms of overall survival, statistically significant differences in favour of tocilizumab were reported also in the subgroup of patients:

- requiring mechanical ventilation, (HR=0.63, [95% CI, 0.46; 0.85]; p=0.0029) and
- aged <65 years (HR=0.64, [95% CI, 0.44; 0.94]; p=0.023),
- with CRP ≥15 mg/dL, a statistically significant increase of OS in patients receiving tocilizumab was observed (HR=0.48, [95% CI, 0.30; 0.77]; p=0.0025).

However, statistically significant differences were not observed in the subgroup of patients aged ≥65 years (HR=0.71, [CI 95%, 0.48; 1.04]; p=0.079) and CRP <15 mg/dL (HR=0.92, [CI 95%, 0.57; 1.48]; p=0.73).

Interpretation of the results should take into account the identified limitations:

- study design – retrospective observational study;
- unbalanced allocation of confounders – the impact of known confounders was reduced by using propensity score matching;
- possible incorrect data classification – due to manual selection of data from electronic databases;
- patient selection error – patients with incomplete data were excluded from the study;
- limited use of the study data for other geographical regions – the study population was limited to citizens of New Jersey, USA;
- risk of selective allocation of patients to tocilizumab treatment;
- qualifying patients with a more severe condition and greater risk of a severe course of the infection to tocilizumab treatment for ethical reasons;
- risk of sampling bias – a discretionary sample was adopted in order to obtain results more quickly.

3.1.4. Study conducted on the Polish population

Tomasiewicz 2020

During the conducted search, Tomasiewicz 2020, a single-arm, retrospective multi-centre study (7 study sites in Poland) was found; the study assessed the effectiveness and safety of tocilizumab in patients with severe COVID-19 requiring oxygen therapy. The study assessed the impact of using tocilizumab on the change of clinical status (assessed subjectively by the attending physician), results of imaging and laboratory tests.

It should be noted that Tomasiewicz 2020 did not meet the predefined inclusion criteria for the review (single-arm retrospective study, sample <100 patients), however, due to the fact that it is the only study conducted on the Polish population, a decision was made to include that study in the review.

28 patients with the mean age of 61.7 ±12.4 years were included in the study. The average time from symptom onset to the first dose of tocilizumab was 10.5 ± 5.7 days. Clinical improvement assessed by the attending physician was reported within 24 hours of tocilizumab administration in 11 (39%) patients, within 1 week in 23 (82%) patients and within a fortnight in 25 (89%) patients; no change in the course of the study was reported in one (4%) patient, whereas two (7%) patients died.

Twelve patients (43%) no longer required oxygen therapy after one week of tocilizumab administration ($p<0.001$). Median oxygenation prior to TCZ administration was 88% and after 10 days it increased to 97%. Mechanical ventilation was required in five (17%) patients prior to TCZ administration, after administration of the first dose, that number was reduced to 3 patients (11%). After the use of TCZ, the need for mechanical ventilation leading to both death and clinical improvement was associated with <90% baseline oxygenation, and ≥90% baseline oxygenation was associated with lack of mechanical ventilation within or after 24 hours.

Of all the patients covered by the study, 25 had repeated chest X-ray or chest CT during and/or after hospitalisation. Among them, lung changes improved in 21 (84%) patients after at least two weeks (range 2–10 weeks) of treatment, with 19 showing minimal or no changes in the final examination. 59% of these 21 patients showed an improvement in lung changes within 2–8 weeks, and all 21 (100%) had improved after >8 weeks.

Elevated CRP (in all patients at baseline) normalised in 13 (46%) of patients after TCZ administration ($p<0.001$). Median procalcitonin and fibrinogen levels decreased significantly after TCZ treatment ($p\leq0.001$), and IL-6 levels after TCZ to day 3 ($p<0.001$) increased, after which it would start decreasing. Patients with high baseline IL-6 levels took longer to improve clinically or did not improve compared to patients with low IL-6 levels (25% vs. 19%; $p>0.05$). Lymphopaenia (<1.5 × 109/L) was observed in 24 (86%) patients before tocilizumab and in 15 (54%) patients after tocilizumab ($p=0.041$).

The activity of alanine aminotransferase increased slightly after tocilizumab treatment ($p\leq0.022$); similarly, the median QTc interval increased from 426 ms (402–450) before tocilizumab to 431 ms (412–449; $p=0.012$) after tocilizumab. One patient had markedly increased systolic blood pressure (220 mg Hg) following tocilizumab treatment.

Interpretation of the results should take into account the identified limitations:

- retrospective nature of the study;
- a small, heterogeneous patient population (the patients suffered from various co-morbidities, received other therapies simultaneously);
- no blinding of the investigators;
- lack of control group due to the lack of admitted standard of care with proven efficacy in COVID-19 treatment;
- no information about the adjuvant treatment used;
- no objective assessment of the patients' clinical status (the clinical status was assessed subjectively by the attending physician).

3.1.5. Primary studies: summary of results

Table 5 presents results of primary studies for the analysed outcomes. Additionally, a comparison of the results of the primary studies in terms of mortality rate was carried out, with the assessment of the significance of the result and the level of reliability of the scientific evidence.

Table 5. Controlled experimental and observational studies

No.	Study author, year / acronym	Reliability level	Test arm, N	Control arm, N	Death	Survival probability post-intubation	ICU admission	ICU stay	Time to hospital discharge	Clinical deterioration
1.	**COVACTA (Rosas 2020)**	**C**	TCZ + SoC	PLC + SoC			p=0.01	p=0.045	HR=1.35 (95%CI:1.02; 1.79)	HR=0.614 (95% CI: 0.4; 0.94)
2.	**Biran 2020**	**E**	TCZ + HCQ, HCQ, AZM, GCs	HCQ, AZM, GCs	HR=0.71 (95% CI: 0.56; 0.89) <65 years HR=0.64 (95% CI: 0.44; 0.94) CRP ≥ 15 mg/dL HR=0.48 (95% CI: 0.30; 0.77) Mechanical ventilation HR=0.63 (95% CI: 0.46; 0.85)					
3.	**Carvalho 2020**	**E**	TCZ + SoC	SoC						
4.	**Guaraldi 2020**	**E**	TCZ + SoC	SoC	p=0.0001					
5.	**Ip 2020**	**E**	TCZ	No TCZ						
6.	**Somers 2020†**	**E**	TCZ	SoC	At day 14 of follow-up: 7 (9%) vs. 20 (26%), p=0.005 At day 21 of follow-up: 11 (14%) vs. 25 (33%), p=0.006 At day 28 of follow-up: 14 (18%) vs. 27 (36%), p=0.01	HR_0=0.50 [0.27, 0.90] HR_2=0.55 [0.33, 0.90] HR_3=0.54 [0.35, 0.84] HR_1=0.54 [0.29, 1.00]				OR_0, OR_1* OR_2=0.59 (95% CI: 0.36; 0.95)* OR_3=0.61 (95% CI: 0.40; 0.92)*

† *0 –Non-adjusted; 1 – Model A: demographic adjustment; 2 – Model B: demographic adjustment + IPTW (inverse probability of treatment weights); 3 – Model C: demographic adjustment + IPTW-Mi (multiple imputation); * Clinical status deterioration by one level on the six-level illness severity ordinal scale*

AZM – azithromycin, CSs – corticosteroids, HCQ – hydroxychloroquine, MV – mechanical ventilation, SoC – standard of care, PLC – placebo; TCZ – tocilizumab

Efficacy analysis for reducing the risk of death

The analysis included results of 5 studies (4 observational, 1 quasi-experimental) which assessed mortality risk reduction after tocilizumab treatment. Statistically significant differences were reported in 3 studies: Biran 2020, Guaraldi 2020 and Somers 2020, which indicated mortality risk reduction in the tocilizumab arm by approx. 40%, 70% and 15%, respectively.

It should be underlined that in the studies included in the analysis, the control arm received standard of care, however, depending on the publication, it involved different interventions and active substances (i.a. hydroxychloroquine, azithromycin) or combination therapies. At the same time, not all studies determined what health technologies were used in the control arm.

Table 6. Summary of data on mortality – tocilizumab

Study	Test arm, n/N (%)	Control arm, n/N (%)	Result, relative parameter (95% CI)	Reliability level
COVACTA (Rosas 2020)	56/294	28/144.	OR=0.975 (0.588–1.615)	**C**
Biran 2020	102/210	256/420.	**OR=0.605 (0.433–0.845)**	**E**
Carvalho 2020	5/29	4/24.	OR=1.042 (0.246–4.408)	**E**
Guaraldi 2020	13/176	73/365.	**OR=0.319 (0.172–0.593)**	**E**
Ip 2020	62/134	231/413.	OR=0.678 (0.459–1.003)	**E**
Somers 2020	14/78	27/76.	**OR=0.397 (0.188–0.836)**	**E**

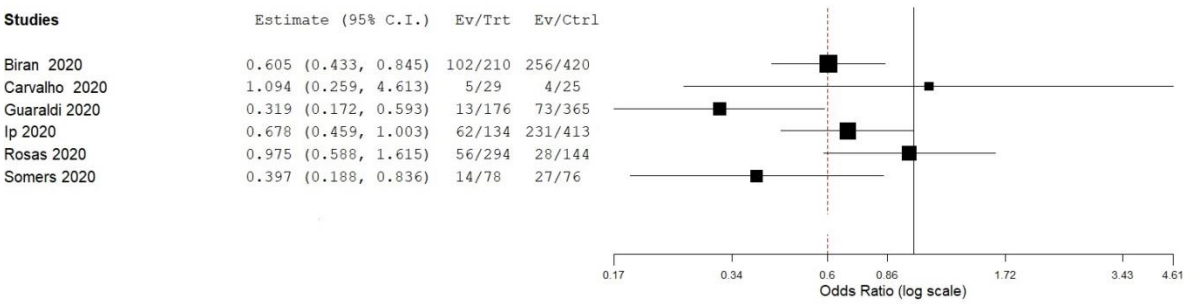

Figure 1. Analysis of studies for the TCZ+SoC vs. SoC comparison expressed as the odds ratio

3.2. Results of secondary studies

2 secondary studies constituting systematic reviews with a meta-analysis were identified as part of the systematic review: Boregdowa 2020 and Lan 2020.

Furthermore, a conducted non-systematic search identified a monitoring report of EUnetHTA (Project ID: RCR 03) which assessed the efficacy and safety of tocilizumab used in COVID-19 treatment.

Boregdowa 2020 qualified sixteen studies (13 retrospective and 3 prospective studies), with a total population of 3,641 patients (64% men). Standard of care was received by 2,488 patients (61.7%), and tocilizumab by 1,153 patients (68.7%).

The fatality rate in the tocilizumab arm was 22.4% (258/1,153) and was lower than in the standard of care arm: 26.21% (652/2,488) (OR=0.57 [95% CI, 0.360; 0,92], p=0.02). A high heterogeneity of the included studies was noted (80%).

It was also observed that European studies did not demonstrate a significant difference in terms of mortality between the TCZ and SoC arms (n=10; OR 0.52 [95% CI 0.23; 1.17], p=0.12). However, US studies demonstrated lower mortality in the TCZ arm compared to SoC (n=6; OR=0.61 [95% CI 0.46; 0.79] p<0.01). According to the authors that might have been related to the shortage of beds in the ICU in Italy and the rapid increase of COVID-19 cases (the majority of European studies were from Italy, which indicates that the availability of resources can significantly impact outcomes).

According to authors of the review, the use of tocilizumab can reduce the risk of death in patients with severe COVID-19. The need for drawing conclusions on the role of TCZ in the treatment of severe COVID-19 based on high quality prospective clinical trials, including RCTs, is indicated.

The following limitations of the review have been identified:

- the majority of the included studies were retrospective observational studies, no RCTs were included;
- the majority of the included studies were from Italy and the United States – the results should not be generalised;
- no assessment of the heterogeneity of the primary studies (differences in terms of the administered antiviral treatment and reported co-morbidities), high statistical heterogeneity of the cumulated result.

7 retrospective studies (592 patients: 240 in the intervention arm and 352 in the control arm) were included in Lan 2020.

Mortality was reported in all studies and was 16.3% (39/240) in the tocilizumab arm for patients with severe COVID-19, however, the results were not statistically significant (RR=0.62 [95% CI 0.31; 1.22]; I^2=68%). The risk of ICU transfer (reported in 5 studies) was 35.1% in the tocilizumab arm and 15.8% in the control arm (RR=1.51 [95% CI 0.33; 6.78] I^2=86%). The use of mechanical ventilation (reported in 3 studies) in the intervention arm and the control arm was, respectively: 32.4% vs. 28.6% (RR=0.82 [95% CI 0.14; 4.94] I^2=91%).

The authors of the Lan 2020 review underline that there is no conclusive evidence (low-quality evidence) that tocilizumab would provide additional benefits in the treatment of patients with severe COVID-19. According to the authors, continued use of tocilizumab in COVID-19 cases should be suspended until high quality evidence from randomised clinical trials are available.

<u>Several limitations of the review have been identified:</u>

- only retrospective studies have been included;
- heterogeneous clinical status of the patients included in the studies;
- in addition to two studies which attempted to match the test arm to the control arm in terms of disease severity, the tocilizumab arm consistently had more severe symptoms compared to the control arm in most of the studies included in the meta-analysis;

- the studies used a variety of treatment regimens, including different dosage and frequency of tocilizumab administration;
- the number of studies and patient samples was small and may result in type II bias.

When assessing the efficacy and safety of tocilizumab therapy, the authors of the EUnetHTA monitoring report included: 1 RCT (Salvarani 2020) and 5 observational studies. In the case of the RCT, there are not sufficient data from clinical trials with regard to using tocilizumab in COVID-19 patients – Salvarani 2020 was discontinued prematurely due to failure to demonstrate clinical benefits of TCZ in terms of mortality and only initial results were published.

Only the safety of the intervention was assessed based on the observational studies; the main adverse reaction reported during tocilizumab treatment consisted in elevated liver enzyme levels. Neutropaenia or thrombocytopaenia were uncommon. Additional adverse events such as the risk of serious infections (e.g. tuberculosis, other bacterial pathogens) have only been reported in the context of continued tocilizumab administration. No adverse reactions were observed during treatment in a retrospective analysis of data from 21 patients (Xu 2020). During a 10-day follow-up in Toniati 2020, the investigators reported three cases of serious adverse events: two patients experienced septic shock and death, one patient experienced gastrointestinal perforation requiring urgent surgery; at day 10 of follow-up, the patient was alive.

A summary of the primary studies included in the AOTMiT's review and the identified secondary studies, as well as the EUnetHTA monitoring report, is presented in Table 7.

Table 7. A summary of primary studies included in to the AOTMiT's review and secondary studies included in the analysis.

Study	AOTMiT	Boregowda 2020[8]	Lan 2020[9]	EUnetHTA 2020[10]
Biran 2020	+	-	-	-
Campochiaro 2020	-*	+	-	-
Capra 2020	-*	+	+	-
Carvalho 2020	+	-	-	-
Colaneri 2020	-*	+	+	-
Garcia 2020	-$	+	-	-
Guaraldi 2020	+	+	-	-
Ip 2020	+	+	-	-
Kewan 2020	-*	+	-	-
Klopfenstein 2020	-*	+	+	-
Luo 2020	-†	-	-	+
Martinez-Sanz 2020	-$	+	-	-
Mikulska 2020	-*	+	-	-
Quartuccio 2020	-*	+	+	-
Ramaswamy 2020	-$	+	+	-
Rojas-Marte 2020	-*	+	-	-
Roumier 2020	-$	+	+	-
Rosas 2020	+	-	-	-
Rossi 2020	-*	-	-	+
Salvarani 2020	-#	-	-	+
Somers 2020	+	+	-	+
Toniati 2020	-†	-	-	+
Wadud 2020	-$	+	+	-
Xua 2020	-†	-	-	+

* The reason for exclusion from the analysis is specified in table 17.

$ The study does not meet the inclusion criteria for the analysis (population of the intervention arm <100 patients)

$ The study does not meet the inclusion criteria for the analysis (single-arm study)

The study was discontinued; full results have not been published

4. CONCLUSIONS

In view of the evidence on other viruses, one can assume that tocilizumab therapy can play a certain role in fighting the COVID-19 pandemics. However, the findings from the analysis of the studies identified in the course of the conducted search are inconclusive.

Results of the randomised, double-blind clinical trial suggest that tocilizumab did not impact the change of clinical status measured using a 7-category ordinal scale and on mortality reduction (COVACTA). Statistically significant benefits of using tocilizumab were observed with regard to duration of hospital stay (20 vs. 28 days), duration of ICU stay and the need for an ICU transfer. Furthermore, statistically significant results with regard to the risk of failure of the implemented treatment were reported in patients not requiring mechanical ventilation at randomisation.

Results of observation studies on TCZ efficacy in terms of mortality risk reduction are inconsistent – results of 3 studies (Somers 2020, Biran 2020, Gualardi 2020) of the 5 studies which report results for this outcome indicate statistically significant differences in favour of TCZ as compared to SoC. Results of the identified clinical trials should be interpreted with caution. Uncertainty of estimates in COVACTA results from the differences between the study arms in terms of the supportive treatment implemented (corticosteroids and antiviral treatment), uncompleted follow-up, the adopted manner of result analysis and the pre-print nature of the publication. Observational studies involve small patient samples, the arms are not well-balanced with regard to confounding factors, the follow-up duration is frequently insufficient to allow for demonstrating differences between the interventions. The differences in the baseline patient characteristics hinder drawing conclusions on the actual benefits of using TCZ.

Safety of the intervention in question was reported in three studies:

- Rosas 2020: no statistically significant differences in the TCZ vs. standard of care comparison (at day 28 of follow-up) in terms of adverse reactions in general and serious adverse reactions were reported;
- Carvalho 2020: no adverse events which could be directly associated with tocilizumab administration have been reported;
- Guaraldi 2020: adverse events were closely monitored during the study period: in the tocilizumab arm, one patient (<1%) had a TCZ injection site reaction which resolved spontaneously within a few hours; one episode (<1%) of severe neutropaenia required administration of granulocyte colony-stimulating factor; there was no evidence of a difference in the rate of aspartate aminotransferase increase between the treatment arms.

Authors of the EUnetHTA monitoring report indicate that elevated liver enzymes were the key irregularity reported during tocilizumab treatment.

APPENDIX

Table 8. Description of the methodology and results of Rosas 2020 (COVACTA) – tocilizumab

Rosas 2020 (COVACTA)					
Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
International, multi-centre, randomised, double-blind, phase 3 COVACTA study Duration of the study: 03/04/2020–28/07/2020 Objective: efficacy and safety of tocilizumab in patients with severe COVID-19	N=438 (2:1 randomisation) Inclusion criteria: 18 years or older; COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or computed tomography Exclusion criteria: Blood oxygen saturation ≤93% or partial pressure of oxygen/fraction of inspired oxygen <300 mm/Hg. Additionally, patients were excluded if the treating physician determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2. Standard of care per local practice (antiviral treatment, low-dose steroids, convalescent plasma, supportive care) was permitted. However, concomitant treatment with another investigational agent (except antivirals) or any immunomodulatory agent was prohibited.		Ni = 294 Intravenous tocilizumab (8 mg/kg infusion, maximum 800 mg) + standard of care	Nc=144 Placebo + standard of care	• Pre-print status • The lack of standardised treatment across study sites • More patients in the placebo arm than the tocilizumab arm received concomitant steroids, which might have created bias toward lower mortality in the placebo arm
	Men, n (%):		205 (69.7)	101 (70.1)	
	Age, years, average		60.9 ± 14.6	60.6 ± 13.7	
	Co-morbidities, n (%):	≥1 co-morbidity	231 (78.6)	124 (86.1)	
		Obesity	63 (21.4)	27 (18.8)	
		Diabetes	105 (35.7)	62 (43.1)	
		Cardiovascular diseases	88 (29.9)	35 (24.3)	
		Hypertension	178 (60.5)	94 (65.3)	
		Hepatic impairment	6 (2.0)	2 (1.4)	
		Chronic lung disease	49 (16.7)	22 (15.3)	

Results					
Outcome	**Observation time (days)**	**Intervention**	**Control**	**Relative parameter (95% CI) / p**	**Absolute NNT parameter (95% CI)**
Clinical status (7-category ordinal scale*), category, median	28	1 (1–1)	2 (1–4)	OR=1.19 [0.81–1.76], p=0.36	-
	14	3 (2–4)	4 (3–5)	OR=1.42 [0.99–2.05], p=0.05	-
Mortality, n (%)	28	58 (19.7%)	28 (19.4%)	p=0.94	-
Time to hospital discharge, days, median	-	20 (17–27)	28 (20–NE)	**HR=1.35 [1.02–1.79], p=0.037**	-

Rosas 2020 (COVACTA)					
Time to improvement of ≥2 categories on a 7-category ordinal scale of clinical status, days; median	-	14 (12–17)	18 (15–28)	HR=1.26 [0.97–1.64], p=0.08	-
Duration of ICU stay, days, median	-	9.8 (7–15.7)	15.5 (8.7–25.5)	**p=0.045**	-
Transfer to the ICU of patients not in ICU at baseline, n/N (%)	28	30/127 (23.6)	26/64 (40.6)	**RR=0.58 [0.38–0.90]^, p=0.01**	**6 (3;31)^**
Ventilator-free days to day 28, median	28	22.0 (18.0–28.0)	16.5 (11.0–26.0)	p=0.32	-
Incidence of mechanical ventilation among patients not on mechanical ventilation at randomisation, n/N (%)	28	51/183 (27.9)	33/90 (36.7)	p=0.14	-
Clinical failure ** among patients not on mechanical ventilation at randomisation, n/N (%)	28	53/183 (29.0)	38/90 (42.2)	**HR=0.614 [0.4–0.94**], **p=0.03**	**8 (7;78)^**
Patients with ≥1 adverse event, n (%)	28	228/295 (77.3)	116/143 (81.1)	RR=0.95 (0.86–1.05)^	–
Adverse events, n	28	778/295	360/143		
Patients with ≥1 serious adverse event, n (%)	28	103/295 (34.9)	55/143 (38.5)	RR=0.91 (0.70–1.18)^	–
Serious adverse events, n	28	160/295	101/143		
Infections, n (%)	28	113/295 (38.3)	58/143 (40.6)		
Serious infections, n (%)	28	62/295 (21.0)	37/143 (25.9)		
Bleeding events, n (%)	28	45/295 (15.3)	16/143 (11.2)		
In this randomised placebo-controlled trial in hospitalised COVID-19 pneumonia patients, tocilizumab did not improve clinical status or mortality. Potential benefits in time to hospital discharge and duration of ICU stay are being investigated in ongoing clinical trials.					

**1=discharged or ready for discharge; 2=non–ICU hospital ward, not requiring supplemental oxygen; 7=death*
*** Death, withdrawal during hospitalisation, transfer to ICU, or requirement for invasive mechanical ventilation within 28 days of baseline*
**** Alanine aminotransferase or aspartate aminotransferase levels >3× upper limit of normal with either bilirubin level >2× upper limit of normal.*
^ Agency's own calculations

Table 9. Description of the methodology and results of Biran 2020 – tocilizumab

Biran 2020					
Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Retrospective, observational, multi-centre cohort study Duration of the study: 01/03/2020-24/02/2020 Country: USA Objective: to investigate the association between tocilizumab exposure and in-hospital mortality among patients requiring intensive care unit (ICU) support for COVID-19	Unmatched patients (n=764) Propensity score-matched patients (n=630)* Generating a matched cohort in a 1:2 ratio to pair one patient with tocilizumab treatment to two patients who did not receive tocilizumab. <u>Inclusion criteria:</u> Adult patients (aged ≥18 years) with RT-PCR-confirmed SARS-CoV-2 who were hospitalised at one of Hackensack Meridian Health's 13 hospitals during the study period and required ICU support. Patients receiving tocilizumab for chronic rheumatological conditions were not excluded. <u>Exclusion criteria:</u> Pregnant patients and participants in a clinical therapeutic trial		Propensity score-matched patients: Ni = 210 <u>Treatment:</u> Tocilizumab + SoC Of 210 patients in the propensity score-matched population who received tocilizumab, 206 (98%) received 400 mg flat dosing, two (1%) received 8 mg/kg, and two (1%) received other doses; 185 (88%) received one infusion and 25 (12%) received a second infusion.	Propensity score-matched patients: Nk = 420 <u>Treatment:</u> SoC	• Possible misclassification of data • Limited applicability to other geographical regions • Possible sampling bias
	Men, n (%):		155 (74)	281 (67)	
	Women, n (%)		55 (26)	139 (33)	
	Age, median (IQR):		62 (53-71)	65 (56-74)	
	Combined treatment	Steroids, n (%)	97 (46)	191 (45)	
		Hydroxychloroquine, n (%)	199 (95)	355 (85)	
		Azithromycin, n (%)	141 (67)	213 (51)	
		Hydroxychloroquine and azithromycin, n	137 (65)	193 (46)	
	Number of co-morbidities, n (%)†	0	30 (14)	68 (16)	
		1	68 (32)	99 (24)	
		2	50 (24)	106 (25)	
		≥3	62 (30)	147 (35)	
	Co-morbidities, n (%)	Diabetes	77 (37)	158 (38)	
		COPD or asthma	30 (14)	61 (15)	
		Hypertension	122 (58)	254 (60)	
		Coronary disease	29 (14)	73 (17)	
		Arrhythmia	13 (6)	42 (10)	
		Cancer	20 (10)	49 (12)	
		Body mass index ≥30 kg/m²	76 (36)	14 (3)	

Results						
Outcome		**Observation time (days)**	**Intervention**	**Control**	**Relative HR parameter (95% CI) / p**	**Absolute parameter**
Overall survival	Propensity score-matched patients, % (n/N)	22 days (IQR: 11--53)	49 (102/210)	61 (256/420)	**0.71 (0.56;0.89), p=0.0027**	-
	< 65 years (n=307)				**0.64 (0.44;0.94), p=0.023**	-
	≥ 65 years (n=312)				0.71 (0.48;1.04), p=0.079	-
	CRP < 15mg/dL (n=272)				0.92 (0.57;1.48), p=0.73	-
	CRP ≥ 15 mg/dL (n=286)				**0.48 (0.30;0.77), p=0.0025**	-
	Mechanically ventilated (n=587)				**0.63 (0.46;0.85), p=0.0029**	-
Death, % n/N		22	49 (102/210)	61 (256/420)	**OR=0,605 (0,433–0,845)^**	-
Median overall survival, days		22	not reached (23-NR)	19 (16-26)	**0.71 (0.56;0.89), p=0.0027**	-
Overall survival adjusted for time from drug administration, days		22	Not reached (18-NR)	19 (16-26)	p=0.0784	-

*13 variables were used for propensity score matching: age, gender, diabetes, COPD or asthma, hypertension, cancer, renal failure, obesity, oxygenation <94%, qSOFA score, use of steroids, C-reactive protein >15 mg/dL, and intubation or mechanical ventilator support. Hosmer and Lemeshow goodness-of-fit test, p=0·51;†Number of co-morbidities from diabetes, COPD or asthma, hypertension, coronary disease, cerebrovascular disease, heart failure, arrhythmia, cancer, renal failure, rheumatological disorder, and body-mass index ≥30 kg/m². COPD = chronic obstructive pulmonary disease

Table 10. Description of the methodology and results of Carvalho 2020 – tocilizumab

Carvalho 2020				
Effects of Tocilizumab in Critically Ill Patients With COVID-19: A Quasi-Experimental Study				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Single-centre, quasi-experimental study Duration of the study: 21/03/2020 – 31/05/2020 Follow-up continued through June 7th or a minimum of 14 days for all patients. Objective: effect of tocilizumab on in-hospital mortality and development of positive cultures in patients with COVID-19 admitted to the ICU.	N=53 All the patients admitted to the ICU with suspected COVID-19 underwent diagnostic testing for SARS-CoV-2 through nasopharyngeal swabs. The patients admitted to the ICU also received respiratory support with either oxygen through a nonrebreather mask or non-invasive or mechanical ventilation. Patients with acute respiratory distress syndrome (ARDS) were managed with neuromuscular blockade and a protective ventilation strategy that included low tidal volume (6 mL/kg of predicted body weight) and driving pressure (less than 15 cmH2O) as well as optimal PEEP calculated based on the best lung compliance. Exclusion criteria: Patients with primary or secondary immunodeficiency, using immunosuppressive drugs, pregnant women, patients without respiratory symptoms and in palliative care.	n=29 Tocilizumab 400 mg IV two doses + SoC After IRB approval and availability of tocilizumab, all consecutive adult patients (age > 18 years) admitted to the ICU with suspected or confirmed SARS-CoV-2 infection plus fever (axillary temperature >38ºC) or elevated CRP (≥5 mg/dL) and ventilatory or oxygenation deterioration or need for ventilatory support (non-invasive or mechanical ventilation) received two 400 mg doses of intravenous tocilizumab.	n=24 Patients admitted to the ICU prior to tocilizumab being available.	• Non-blinded • No randomisation • Small sample size • Corticosteroid use was not balanced between the arms, limiting the determination of the actual benefit in oxygenation and CRP reduction of tocilizumab in patients who used corticosteroids
		Standard intensive medical care, as per clinical protocol of the specific facility, which includes hydroxychloroquine and azithromycin. Corticosteroids in accordance with specific clinical indications (e.g. acute respiratory distress syndrome).		
	Median age, years	55 (44–65)	58.5 (51–70.8)	
	Men, %	62	75	
	Corticosteroid use	24 (83), p = 0.001	9 (37), p=0.001	
	SAP III at admission	43 (3–-55)	45 (38.8–54);	
	Median days from symptom occurrence to admission, days	6 (5–8)	8 (5–10);	
	Mechanical ventilation, n (%)	15 (52)	7 (29)	
	Use of HCQ+AZM, n (%)	22 (76)	17 (71)	
	WBC, n/mm3	7200 (5700–9500)	6500 (5375–9575)	
	CRP, mg/dL	19.5 (8.18–28.2)	15.8 (6.28–20.3)	
	LDH, U/L	497 (379.8–656.5)	347 (291–511)	
	D-dimer, ng/mL	1128.5 (518–1501.7)	1514.5 (798.5–2470.5)	
	Ferritin, ng/mL	1124.5 (644.3–1539.7)	871.7 (432.8–1509.6)	

Results					
Outcome	**Observation time (days)**	**Intervention**	**Control**	**Relative parameter (95% CI) / p**	**Absolute parameter**
Mortality, n (%)	–	5 (17)	4 (17)	p=1	–

Carvalho 2020					
Any positive culture, n (%)	–	11 (38)	4 (17)	p=0.13	–
Bacterial positive culture, n (%)	–	10 (34)	3 (12)	p=0.1	–
Fungal positive culture, n (%)	–	6 (21)	1 (4)	p=0.12	–
Use of ATB, n (%)	–	19 (66)	15 (63)	p=1	–
Need of RRT, n (%)	–	9 (31)	3 (13)	p=0.18	–
CRP (mg/dL), median (IQR)	1	20.8 (15.5–36)	13.5 (5–17.25)	p=0.0005	–
	2	22.4 (15.18–28.15)	7 (5.25–8.4)	p=0.001	–
	3	14.3 (5.5–22.3)	4.9 (3.8–11.3)	p=0.023	–
	4	4.75 (3.08–8.1)	3.5 (2.75–15.63)	p=0.44	–
	5	2.8 (2.1–5.2)	5 (2.13–7.75)	p=0.07	–
CRP (mg/dL) – logistic regression model	–	–	–	p=0.009	–
WBC/mm^3, median (IQR)	1	9600 (7350-14650)	6900 (5000–9025)	p=0.08	–
	2	8500 (5600-12700)	7500 (5350–10200)	p=0.87	–
	3	7300 (4800-11000)	6100 (5300–9150)	p=0.45	–
	4	8700 (6800-11850)	7050 (5375–13125)	p=0.8	–
	5	10100 (6400-14650)	7900 (6625–15525)	p=0.9	–
WBC/mm^3– logistic regression model	–	–	-	p=0.02	–
PaO_2/FiO_2 ratio (normalised)	1	1	1	–	–
	2	1.11 (0.91–1.41)	1 (0.98–1.04)	p=0.043	–
	3	1.42 (0.89–1.82)	1 (0.91–1.23)	p=0.02	–
	4	1.2 (1.04–1.53)	1 (0.95–1.59)	p=0.14	–
	5	1.25 (1.17–1.72)	1.06 (0.99–1.53)	p=0.07	–
PaO_2/FiO_2 to SpO_2/FiO_2 ratio – logistic regression model	–	–	–	p=0.02	–
Safety: No adverse events were reported that could be directly related to the administration of tocilizumab.					
CRP – c-reactive protein; HCQ+AZM – hydroxychloroquine plus azithromycin; LDH – lactate dehydrogenase; SAPS – simplified acute physiology score; WBC – white blood cells; IRB – Institutional Review Board					

Table 11. Description of the methodology and results of Guaraldi 2020 – tocilizumab

Guaraldi 2020					
Tocilizumab in patients with severe COVID-19: a retrospective cohort study					
Methodology	**Population**	**Intervention**		**Control**	**Limitations**
Retrospective, observational cohort study Duration of the study: 21/02/2020–24/03/2020 and 21/03/2020–30/04/2020 Objective: to assess the role of tocilizumab in reducing the risk of invasive mechanical ventilation and death in patients with severe COVID-19 pneumonia who received standard of care treatment.	N=544 Inclusion criteria: Adults (≥18 years) with COVID-19, confirmed by PCR on nasopharyngeal swab. Patients with severe pneumonia, defined as at least one of the following: presence of a respiratory rate of 30 or more breaths per minute, peripheral blood oxygen saturation (SaO2) of less than 93% in room air, a ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) of less than 300 mm Hg in room air, and lung infiltrates of more than 50% within 24–48 h, according to Chinese management guidelines for COVID-19 (version 6.0). Exclusion criteria (for the use of tocilizumab): Coexistent infections other than COVID-19; a PaO2/FiO2 ratio greater than 300 mm Hg; chronic or current glucocorticoid use; history of severe allergic reactions to monoclonal antibodies; less than 500 per μL neutrophils or less than 50×10^9 platelets; active diverticulitis, inflammatory bowel disease, or another symptomatic gastrointestinal tract condition that might predispose patients to bowel perforation; severe haematological, renal, or liver function impairment.	Tocilizumab plus standard of care* (overall=179): subcutaneous (n=91); intravenous (n=88) In addition to receiving the standard of care treatment, a non-randomly selected subset of patients also received tocilizumab treatment. Tocilizumab was given either intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (i.e. 324 mg in total), when the intravenous formulation was unavailable.		Standard of care* (n=365)	• Retrospective study. • Short follow-up period, the authors were not able to assess long-term safety and adverse effects.
	Age, years	64 (54-72)		69 (57-78)	
	Men, n (%):	127 (71)		232 (64)	
	Baseline PaO2/FiO2, mmHg	169 (106-246)		277 (191-345)	
	Baseline SOFA score	3 (2-4)		2 (0-3)	
	Duration of symptoms, days from symptom onset	7 (4-10)		5 (2-9)	
	Co-morbidities in patients from the centre in Modena	**TCZ (i.v.) (n=84)**	**TCZ (s.c.) (n=48)**	**SoC (n=222)**	
	All co-morbidities, n (%)	39 (46)	24 (50)	36 (16)	
	Diabetes, n (%)	11 (13)	6 (13)	7 (3)	
	Hypertension, n (%)	37 (44)	22 (46)	30 (14)	
	Cardiovascular diseases, n (%)	9 (11)	6 (13)	12 (5)	
	Chronic renal failure, n (%)	2 (2)	5 (10)	7 (3)	

Results							
Outcome	**Observation time (days)**	**Intervention (n=179)**			**Control (n=365)**	**Relative parameter (95% CI) / p**	**Absolute parameter**
		Subcutaneously (n=91)	**Intravenously (n=88)**	**Overall (n=179)**			
Follow-up, days	–	12 (6–17)	13 (7–18)	12 (6–17)	8 (4–14)	p<0.0001	–
Mechanical ventilation, n (%)	–	17 (19)	16 (1)	33 (18)	57 (16)	p=0.41	–
Deaths in mechanically ventilated patients, n (%)	–	2 (12)	3 (19%)	5 (15)	14 (25)	p=0.51	–
Death †	–	7 (8)	6 (7)	13 (7)	73 (20)	HR_0=0.28 (0.15–0.50), p_0=0.0007 HR_1=0.36 (0.20–0.66), p_1=0.0009 HR_2=0.38 (0.17–0.83), p_2=0.015	–
Data are median (IQR) or n (%), unless otherwise indicated. The p values refer to differences between tocilizumab and standard of care and were calculated using the χ^2 test or Kruskal-Wallis test, as appropriate.							
Safety: Adverse events were carefully monitored during the study period. In the arm, one (<1%) patient had an episode of injection site reaction, with spontaneous resolution in a few hours. One (<1%) episode of severe neutropaenia required granulocyte-colony stimulating factor administration. Finally, there was no evidence for a difference in the rate of increase of aspartate aminotransferase between treatment arms.							

* Standard of care treatment included oxygen supply to target SaO2 reaching at least 90%, hydroxychloroquine (400 mg twice on day 1, followed by 200 mg twice per day on days 2–5, eventually adjusted for creatinine clearance estimated by a chronic kidney disease algorithm), azithromycin (500 mg once per day for 5 days) at the physician's discretion when suspecting a bacterial respiratory super- infection, lopinavir–ritonavir (400/100 mg twice per day) or darunavir/cobicistat (800/150 mg once per day) for 14 days, and low molecular weight heparin for prophylaxis of deep vein thrombosis according to bodyweight and renal function.

† 0 – non-adjusted analysis, 1 – analysis adjusted for age, sex and recruiting centre, 2 – analysis adjusted for age, sex, recruiting centre, duration of symptoms, and Subsequent Organ Failure Assessment (SOFA) score

PaO2/FiO2 – ratio of arterial oxygen partial pressure to fractional inspired oxygen. SOFA – Subsequent Organ Failure Assessment.

Table 12. Description of the methodology and results of Ip 2020 – tocilizumab

Ip 2020					
Hydroxychloroquine and tocilizumab therapy in COVID-19 patients – An observational study					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Retrospective, observational, multi-centre cohort study Duration of the study: 01/03/2020–05/05/2020 Objective: To analyse the effect of hydroxychloroquine in hospitalised patients. The secondary objective was to investigate the effect of tocilizumab in the ICU population.	Hydroxychloroquine therapy analysis: N=2512 Tocilizumab therapy analysis: N = 547 Adult patients aged ≥18 years with COVID-19. Patients were included in the database based on the following inclusion and exclusion criteria: 1) Positive SARS-CoV-2 diagnosis by reverse-transcriptase polymerase chain reaction, 2) hospitalised within the time frame of 01/03/2020 until 05/05/2020, 3) non-pregnant, 4) not on a randomised clinical trial, and 5) did not die during first day of hospitalisation, and 6) were not discharged within 24 hours		n=134 Patients receiving tocilizumab in the ICU Tocilizumab was administered as a single dose in 104 (78%), with the majority receiving 400 mg (96%), followed by 800 mg (1%), 8 mg/kg (1%), 4 mg/kg (1%), and missing dosing (1%).	n = 413 ICU patients who did not receive tocilizumab.	• Retrospective study • Low sample size limited the exploratory tocilizumab analysis.
	Median age, years (IQR)		62 (53–70)	69 (58–77)	
	Men, n (%):		99 (28)	257 (72)	
	Oxygen saturation <94%, n (%)		80 (25)	237 (75)	
	Supportive treatment, n (%)	Glucocorticoids	89 (25)	263 (75)	
		Hydroxychloroquine	128 (26)	358 (74)	
		Azithromycin	126 (30)	293 (70)	
		HCQ+AZM	123 (31)	268 (69)	
	Number of co-morbidities, n (%)	0	19 (27)	51 (73)	
		1	50 (35)	94 (65)	
		2	23 (16)	118 (84)	
		≥3	42 (22)	150 (78)	
	Co-morbidities, n (%)	Diabetes	47 (23)	157 (77)	
		COPD or asthma	20 (22)	69 (78)	
		Hypertension	73 (21)	267 (79)	
		Coronary disease	23 (23)	77 (77)	
		Cerebrovascular disease	4 (15)	22 (85)	
		Tumour	12 (18)	56 (82)	
		Renal failure	8 (15)	47 (85)	
		Rheumatic diseases	3 (16)	16 (84)	
		Body mass index >30 kg/m²	51 (25)	152 (75)	

Results					
Outcome	**Observation time (days)**	**Intervention**	**Control**	**Relative HR parameter (95% CI) / p**	**Absolute parameter**
Mortality, n (%)	30 days	46	56	0.76 (0.57;1.00), p=0.053	-

Table 13. Description of the methodology and results of Somers 2020 – tocilizumab

Somers 2020					
Tocilizumab for treatment of mechanically ventilated patients with COVID-19					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Observational retrospective study Duration of the study: 09/03/2020 – 19/05/2020 Country: USA Objective: comparison of outcomes in patients who received tocilizumab to tocilizumab-untreated controls	N=154 Inclusion criteria: Patients with severe RT-PCR-confirmed COVID-19 requiring invasive mechanical ventilation; ≥ 16 years Exclusion criteria: Intubation not related to COVID-19; inclusion of sarilumab in the clinical trial		Ni=78 Tocilizumab 8 mg/kg (maximum 800 mg) x 1	Nc=76 Standard of care	• Observational retrospective study • Incomplete data for laboratory variables • For patients transferred from outside hospitals, variations in the initial period of care cannot be fully or consistently characterised • Tocilizumab administration was guided by institutional criteria, but was not completely standardised
	Women, n (%)	52 (34)	25 (32)	27 (36)	
	Age, years, average	58 ± 14.9	55 ± 14.9	60 ± 14.5	
	Hypertension	102 (66)	50 (64)	52 (68)	
	Congestive heart failure	36 (23)	16 (21)	20 (26)	
	Chronic lung disease	29 (19)	8 (10)	21 (28)	
	Pre-existing requirement for long term oxygen therapy	4 (3)	1 (1)	3 (4)	
	Diabetes	25 (16)	10 (13)	15 (20)	
	Chronic kidney disease	64 (42)	27 (35)	37 (49)	
	Solid organ transplant	9 (6)	7 (9)	2 (3)	
Results					
Outcome		**Observation time (days)**	**Intervention**	**Control**	**Relative parameter (95% CI) / p**	**Absolute parameter**
Survival probability post-intubation		50	-	-	**HR_0=0.50 [0.27; 0.90], p_0=0.02** HR_1=0.54 [0.29; 1.00], p_1=0.05 **HR_2=0.55 [0.33; 0.90], p_2=0.02** **HR3=0.54 [0.35; 0.84], p3=0.01**	-
Deterioration by one point on a 6-level ordinal scale of illness severity*		28	-	-	OR_0=0.58 [0.33; 1.02], p_0=0.06 OR_1=0.61 [0.34; 1.09], p_1=0.1 **OR_2=0.59 [0.36; 0.95], p_2=0.03** **OR3=0.61 [0.40; 0.92], p3=0.02**	-
Mortality, n (%)		14	**7 (9)**	**20 (26)**	**p=0.005**	-
		21	**11 (14)**	**25 (33)**	**p=0.006**	-
		28	**14 (18)**	**27 (36)**	**p=0.01**	-
Patients discharged before study completion, n (%)		-	**44 (56)**	**30 (40)**	**p=0.04**	-
duration of hospital stay (among the discharged), median		-	20.4 (13.8, 35.8)	22.9 (16.3, 28.5)	p=0.31	-
Duration of mechanical ventilation**, median		-	13.8 (7.1, 27.5)	13.0 (8.1, 23.5)	p=0.94	-
Superinfection, n (%)		-	**42 (54)**	**20 (26)**	**p<0.001**	-
0 – Non-adjusted; Model A: demographic adjusted; Model B: demographic + IPTW (inverse probability of treatment weights) adj; Model C: demographic + IPTW-Mi (multiple imputation) adj ** (1) discharged alive, (2) hospitalised/off ventilator without superinfection, (3) hospitalised/off ventilator with superinfection, (4) hospitalised/mechanically ventilated without superinfection, (5) hospitalised/mechanically ventilated with superinfection, (6) deceased; ** limited to those who were extubated alive during the study period (n=94)*						
Tocilizumab was associated with improved survival, despite higher occurrence of superinfections, in a cohort of COVID-19 patients requiring mechanical ventilation						

Table 14. Description of the methodology and results of Tomasiewicz 2020 – tocilizumab

Tomasiewicz 2020				
Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study				
Methodology	**Population**		**Intervention**	**Limitations**
Retrospective observational study (7 centres across Poland) Duration of the study: 15/03/2020 – 30/04/2020 Objective: assessment of efficacy and safety of tocilizumab in patients with severe COVID-19	N = 28 Patients with severe COVID-19 requiring oxygen therapy Inclusion criteria: Adult patients (aged ≥18 years) with COVID-19 who met the following criteria: cough, dyspnoea, or fever (>38ºC); positive result of a polymerase chain reaction (PCR) test for SARS-CoV-2 from a pharyngeal swab or presence of anti-SARSCoV-2 IgA/IgM antibodies; typical lung changes on chest x-ray or chest computerised tomography; need for continuous oxygen therapy; SpO_2 ≤94% at any time after admission; and serum IL-6 concentration above the upper limit of normal.		N_1=28 Tocilizumab i.v. max single dose of 800 mg, and if there was no clinical improvement, the dose could be repeated after at least 8 hours (applied in 24 patients). The doses ranged from 3.8 mg/kg to 12 mg/kg (first dose, 6.4 ± 1.9 mg/kg; second dose, 6.4 ± 2.1 mg/kg).	• Retrospective nature of the study; • Small and heterogeneous sample (i.e., patients with different comorbidities, different co-treatments); • The investigators were not blinded. • No control arm due to the lack of a registered standard of care with confirmed efficacy in COVID-19; • No clear information about the combination treatment used; • No objective scale for assessing the clinical condition of patients (the clinical condition was assessed by the attending physician)
	Men, n		19	
	Age, average, years		60.7 ± 12.4	
	Positive result of RT-PCR, n		27/28 *	
	Median days from symptom onset to diagnosis, days		4 (2–7)	
	Median days from symptom onset to TCZ administration, days		10.5 ± 5.7	
	Median oxygen saturation (%)		89 (88–93)	
	Need for mechanical ventilation, n		5/28	
	Comorbidities, n (%) **	Hypertension	14 (50)	
		Diabetes	6 (21)	
		Asthma	2 (7)	
		COPD	2 (7)	

Results					
Outcome		**Observation time**	**Intervention**	**Relative parameter (95% CI) / p**	**Absolute parameter**
Clinical status change, n/N (%)[1]	Improvement	24 h of administration	11/28 (39)	-	-
		7 days	23/28 (82)	-	-
		14 days	25/28 (89)	-	-
	No changes		1/28 (4)	-	-
	Death		2/28 (7)	-	-
Required oxygen therapy[2]		7 days	12/28 (43)	**p<0.001**	-
SpO_2 (%)[2]		Day 1	94 (92–97)	**p≤0.001**	-
		Day 10	97 (94–99)		
Required mechanical ventilation, n/N (%)[2]		NDA	3/28 (11)	-	-
Improved lung changes, n/N (%)		min. 2 weeks (2–10 weeks)	21/25 (84)	-	-
CRP concentration was increased (≥5 mg/dL) in all patients before tocilizumab, and normalised (<5 mg/dL) in 13 (46%) patients after tocilizumab (p<0.001). The median concentrations of procalcitonin and fibrinogen decreased significantly after treatment with tocilizumab (p≤0.001). Meanwhile, the concentration of IL-6 increased considerably after treatment with tocilizumab until day three (p<0.001), when it started to decrease. patients with a high (>100 pg/mL) baseline concentration of IL-6 more frequently demonstrated delayed or no improvement compared to those with low IL-6 levels, although the difference was not significant (25% vs. 19%, respectively; p>0.05). Lymphopaenia (<1.5 × 109/L) was observed in 24 (86%) patients before tocilizumab and in 15 (54%) patients after tocilizumab (p=0.041). The median lymphocyte and platelet counts increased significantly after treatment with tocilizumab (p≤0.003).					
The activity of alanine aminotransferase increased slightly after tocilizumab treatment (p≤0.022). The median QTc interval increased from 426 ms (402–450) before tocilizumab to 431 ms (412–449; p=0.012) after tocilizumab. One patient had markedly increased systolic blood pressure (220 mg Hg) following tocilizumab treatment. It was found that patients with at least two chronic diseases were less likely to improve within 24 hours of treatment and are at a higher risk of death.					
The Authors' conclusions suggest that tocilizumab can control the symptoms of severe COVID-19 by reducing the inflammatory response and rapidly improves the clinical status in most patients.					

Search strategy

Table 15. Medline via PubMed

Search number	Query	Results
3	(((COVID 19[Title/Abstract]) OR (((((((((""severe acute respiratory syndrome coronavirus 2"" [Supplementary Concept]) OR (2019-nCoV[Title/Abstract])) OR (Wuhan coronavirus[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (2019 novel coronavirus[Title/Abstract])) OR (COVID-19 virus[Title/Abstract])) OR (coronavirus disease 2019 virus[Title/Abstract])) OR (COVID19 virus[Title/Abstract])) OR (Wuhan seafood market pneumonia virus[Title/Abstract])))) AND ((((((((("tocilizumab" [Supplementary Concept]) OR (tocilizumab[Title/Abstract])) OR (RHPM-1[Title/Abstract])) OR (RG-1569[Title/Abstract])) OR (R-1569[Title/Abstract])) OR (MSB11456[Title/Abstract])) OR (MSB-11456[Title/Abstract])) OR (atlizumab[Title/Abstract])) OR (Actemra[Title/Abstract])) OR (roactemra[Title/Abstract]))	402
2	(((((((("tocilizumab" [Supplementary Concept]) OR (tocilizumab[Title/Abstract])) OR (RHPM-1[Title/Abstract])) OR (RG-1569[Title/Abstract])) OR (R-1569[Title/Abstract])) OR (MSB11456[Title/Abstract])) OR (MSB-11456[Title/Abstract])) OR (atlizumab[Title/Abstract])) OR (Actemra[Title/Abstract])) OR (roactemra[Title/Abstract])	3.589
1	((COVID 19[Title/Abstract]) OR (((((((((""severe acute respiratory syndrome coronavirus 2"" [Supplementary Concept]) OR (2019-nCoV[Title/Abstract])) OR (Wuhan coronavirus[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (2019 novel coronavirus[Title/Abstract])) OR (COVID-19 virus[Title/Abstract])) OR (coronavirus disease 2019 virus[Title/Abstract])) OR (COVID19 virus[Title/Abstract])) OR (Wuhan seafood market pneumonia virus[Title/Abstract])))	46.496

Table 16. Embase via ovid

1. (severe acute respiratory syndrome coronavirus 2 or 2019-nCoV-2 or Wuhan coronavirus or SARS-CoV-2 or 2019 novel coronavirus or COVID-19 virus or coronavirus disease 2019 or COVID19 or Wuhan seafood market pneumonia virus or COVID-19 or COVID 19).ab,kw,ti	44570
2. exp tocilizumab/	12433
3. (tocilizumab or RHPM-1 or RG-1569 or R-1569 or MSB11456 or MSB-11456 or atlizumab or actemra or roactemra).ab,kw,ti,tn.	8341
4. 2 or 3	13027
5. 1 and 4	908

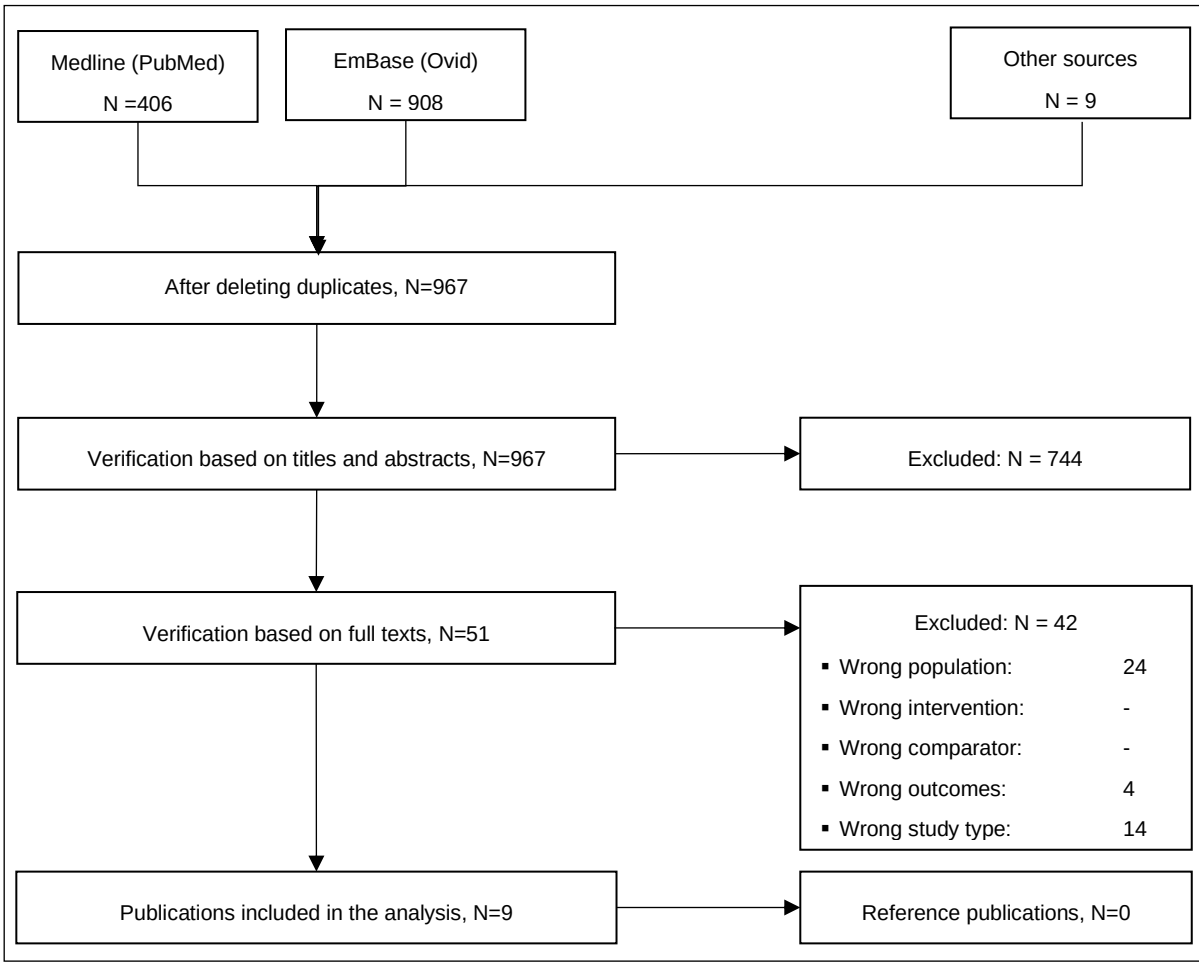

Figure 2. Study selection diagram

Table 17. Studies excluded from the analysis based on full texts.

No.	Publication	Reason for exclusion
1.	**Abdelrahman 2020**	Systematic review without a meta-analysis
2.	**Antwi-Amoabeng 2020**	Systematic review without a meta-analysis
3.	**Berenguer 2020**	Wrong outcomes
4.	**Caillard 2020**	Wrong population
5.	**Campochiaro 2020**	Population in the study arm <100
6.	**Canziania 2020**	Population in the study arm <100
7.	**Capraa 2020**	Population in the study arm <100
8.	**Chastain 2020**	Systematic review without a meta-analysis
9.	**Colaneri 2020**	Population in the study arm <100
10.	**Cortegiani 2020**	Systematic review without a meta-analysis
11.	**Eimer 2020**	Population in the study arm <100
12.	**Hill 2020**	Population in the study arm <100
13.	**Ikonomidis 2020**	Wrong outcomes
14.	**Husain 2020**	Systematic review of single-arm studies
15.	**Kaye 2020**	Systematic review without a meta-analysis
16.	**Kewan 2020**	Population in the study arm <100
17.	**Khiali 2020**	Systematic review without a meta-analysis
18.	**Kimmig 2020**	Systematic review without a meta-analysis
19.	**Klopfenstein 2020**	Population in the study arm <100
20.	**Langer-Gould 2020**	Population in the study arm <100
21.	**Mehta 2020**	Systematic review without a meta-analysis
22.	**Mikulska 2020**	Wrong outcomes
23.	**Moralis 2020**	Population in the study arm <100

24.	**Okoh 2020**	Population in the study arm <100
25.	**Pettit 2020**	Population in the study arm <100
26.	**Perone 2020**	Wrong outcomes
27.	**Potere 2020**	Publication type
28.	**Price 2020**	Study type – single-arm
29.	**Quartuccio 2020**	Population in the study arm <100
30.	**Rodriguez 2020**	Population in the study arm <100
31.	**Rojas-Marte 2020**	Population in the study arm <100
32.	**Roomi 2020**	Population in the study arm <100
33.	**Rossi 2020**	Population in the study arm <100
34.	**Rossotti 2020**	Population in the study arm <100
35.	**Scavone 2020**	Systematic review without a meta-analysis
36.	**Schooling 2020**	Wrong outcomes
37.	**SOLIS-GARCÍA 2020**	Systematic review without a meta-analysis
38.	**Strohbehn 2020**	Population in the study arm <100
39.	**Talaie 2020**	Wrong population
40.	**Tsai 2020**	Population in the study arm <100
41.	**Valenzuela 2020**	Population in the study arm <100
42.	**Zhao 2020**	Publication type

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