A systematic review of Anakinra, Tocilizumab, Sarilumab and Siltuximab for coronavirus-related infections

Authors:

Dr Fasihul Khan. Respiratory Medicine, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, UK

Dr Laura Fabbri. University of Nottingham, Nottingham, UK Respiratory Medicine, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, UK

Dr Iain Stewart. Division of Epidemiology and Public Health, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, UK

Assistant/Associate Professor Karen Robinson. John Hopkins University

Professor Alan Smyth. Division of Child Health, Obstetrics & Gynaecology, University of Nottingham, Nottingham, UK

Professor Gisli Jenkins. Respiratory Medicine, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, UK

Correspondence to:

Dr Fasihul Khan fasihul.khan@nottingham.ac.uk

Abstract

Background

There is accumulating evidence for an overly activated immune response characterised by the release of pro-inflammatory cytokines in severe Covid-19. Suppression of the inflammatory response with immunomodulatory therapies may be a potential therapeutic strategy. We systematically review and assess the effectiveness of specific interleukin-1 and -6 inhibitors for the treatment of coronavirus-related infections.

Methods

Electronic databases, pre-print servers and clinical trial registries were searched to identify current and ongoing studies of immunomodulatory agents (anakinra, sarilumab, siltuximab and tocilizumab) for the treatment of Covid-19 and other coronavirus related super infections. The co-primary outcome was time to hospital discharge (days) and severity on an ordinal scale measured at day 15.

Results

Five retrospective studies (tocilizumab, two case series and two case reports; siltuximab, one case series) were shortlisted for inclusion, totalling 59 patients. All studies had a moderate or high risk of bias, with multiple limitations. Insufficient data and inter-study heterogeneity prevented meta-analysis. Primary outcomes were inconsistently reported but

suggest many patients experienced an improvement in status seven days following therapy. The case fatality ratio (CFR) of patients with severe Covid-19 included in our review was 6.8%, a figure substantially lower than that estimated in non-interventional case series. Of the studies measuring IL-6, all reported elevated baseline levels. Twenty-five ongoing registered clinical trials exploring immunomodulatory agents in Covid-19 were identified, although inconsistency in participants and endpoints are noted.

Conclusion

Inhibition of IL-6 with tocilizumab and siltuximab requires further evaluation in managing the assumed hyperinflammatory response associated with severe Covid-19. These early data are considered hypothesis generating and justify the need for well-designed randomised clinical studies.

PROSPERO registration number: CRD42020176375

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Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China in December 2019[1]. Since then, coronavirus disease 2019 (Covid-19) has been declared a global pandemic by the World Health Organisation (WHO) and continues to spread at an exponential rate[2], with no approved treatments.

The clinical course is typically characterised by a self-limiting flu-like illness, but a subgroup of individuals progress to viral pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS) with poor outcomes. Mechanisms underlying this process are incompletely understood, but accumulating evidence points towards a dysregulated and excessive host immune response. Cytokine storm syndrome, a frequent and subsequent event, is characterised by elevated proinflammatory cytokines including interleukin (IL)-1 and IL-6, and appears to be associated with adverse clinical outcomes[3, 4]. Suppression of these pro-inflammatory cytokines has demonstrated benefit in other virally induced inflammatory diseases, suggesting pharmacological suppression in Covid-19 may also be a potential therapeutic strategy[5].

SARS-CoV-2 appears to share a number of genetic and clinical similarities with other zoonotic coronaviruses, including severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome (MERS)[6, 7]. There are also reports of elevated pro-inflammatory cytokines in patients with SARS and MERS[8, 9], suggesting overlapping therapeutic targets in the management of SARS, MERS and Covid-19.

Through systematic review and critical appraisal of the literature, we assess the effectiveness and safety of specific IL-1 (anakinra) and IL-6 (tocilizumab, siltuximab, sarilumab) inhibitors for the treatment of Covid-19, whilst concurrently drawing on literature from previous similar coronavirus-related super-infections (SARS and MERS). These agents already carry approval for the treatment of other rare non-infectious and autoimmune conditions, with an acceptable safety profile.

Methods

The systematic review was conducted in accordance with a pre-specified protocol (PROSPERO registration number: CRD42020176375), and has been reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[10].

Search strategy and study selection

Electronic database searches were carried out in MEDLINE (1946 to latest) and EMBASE (1974 to latest), and ongoing clinical trial registries (clinicaltrials.gov, EU Clinical Trials Register and the Chinese Clinical Trial Registry), with the last search carried out on 8th April 2020. Due to the expected small number of results, search terms were kept broad, and included keywords and controlled vocabulary for patient and treatment-related terms (see appendix for MEDLINE search strategy). Unpublished and ongoing studies were identified by searching pre-print servers including medRxiv, bioRxiv, ChinaXiv. Searches were carried out independently by two reviewers in a standardised manner which involved screening by titles

and abstracts, followed by full text review. Disagreements were resolved by consensus, with unresolved conflicts decided by a third reviewer.

The review included all original studies including conference abstracts and case reports, evaluating the use of at least one of anakinra, tocilizumab, sarilumab or siltuximab in patients aged over 18 with either suspected or confirmed Covid-19, SARS or MERS. Language or year of publication restrictions was not applied. No minimal study sample size was specified for inclusion.

The planned co-primary outcomes were time to hospital discharge (days) and severity on a six-point ordinal scale at day 15 with the following ratings: i) death; ii) hospitalised on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); iii) hospitalised on non-invasive mechanical ventilation or high flow oxygen devices; iv) hospitalised, requiring supplemental oxygen; v) hospitalised, not requiring supplemental oxygen; vi) not hospitalised. Secondary outcomes included time to clinical improvement (days), duration of mechanical ventilation (days), overall mortality, mortality at 28 days, treatment related adverse events, IL-6 levels (for reviews of IL-6 inhibitors).

Data extraction and risk of bias assessment

Data were extracted from article text and figures using a pre-defined proforma and verified by a second reviewer. Information sought included study design and recruitment strategy, sample size, participant demographics (age, gender, smoking status, comorbidities), clinical investigation findings, intervention characteristics (name of agent, dose, route), treatment

related adverse events, requirement and duration of invasive and non-invasive ventilation, use and dosage of oxygen, duration of intensive care unit (ICU) and hospital stay, survival outcome measures and follow up duration. The pre-specified six-point ordinal primary outcome scale was subsequently adapted to a four-point ordinal scale as outcome detail was inconsistent, i) death; ii) requirement for artificial ventilatory support (NIV/CPAP/IMV); iii) recovery from artificial ventilatory support; iv) discharge. The timing of reported outcomes following therapy was also extracted. For ongoing trial protocols, the registration number, study design, country of study, sample size, key participant eligibility criteria, intervention and comparator details, and primary outcomes were recorded.

Risk of bias assessment was carried out independently in duplicate using the case report/series tool proposed by Murad et al[11]. The tool assesses the risk of basis across eight questions in four domains: selection, ascertainment, causality, reporting. As per the pre-study protocol, all studies were included irrespective of their risk of bias rating.

Statistical analysis

All identified studies (including clinical trial reports) were included in the narrative summary with summary tables for characteristics. Where available, levels of laboratory biomarkers, pre and post-treatment, stratified by patient outcome, were extracted or calculated for quantitative synthesis. Where data were not reported in a tabular format, values were estimated using plotted data. Due to the small number of studies identified, significant inter-study heterogeneity and variation in endpoints, meta-analysis was not possible.

Results

Search of the electronic databases (MEDLINE and EMBASE) on 8th April yielded a total of 228 studies. Following removal of duplicates and screening, three articles were shortlisted for inclusion. Two further studies were identified following a pre-print server search and 25 planned or in-process clinical trials were identified through clinical registry searches (Figure 1). All studies were performed in patients with Covid-19, with no relevant studies identified for SARS or MERS. Individual study characteristics for the published studies are presented in Tables 1 and 2. Primary clinical outcomes are presented in Table 3. Change in IL-6 and C-reactive protein (CRP) levels following treatment is summarised in Table 4 and Figure 2. Currently registered clinical trials are presented in Tables 5-8.

Included studies provided a total of 59 patients, however primary clinical outcomes were inconsistently reported. Where time to hospital discharge was available, patients were hospitalised for an average of 13.5 (±3.1) days following therapy[12], with a similar 17 days reported in a case study[13] (Table 3). Outcomes evaluated on an adapted 4-point ordinal scale indicated that most patients were in recovery seven days following therapy, although timing of records was inconsistent across studies. A total of 20 patients (34%) were discharged during follow up, whilst four died providing an absolute case fatality of 6.8%.

Risk of bias assessment of the five retrieved studies identified multiple limitations and highlighted a number of biases (Table 9). All included studies were either retrospective case series or individual patient case reports, two case series had not undergone peer-review at the time of inclusion. In the majority of case series, there was the possibility of high

selection bias as it was unclear whether consecutive patients receiving the drug at the participating hospital were enrolled, or just a select handful. Many of the studies provided insufficient detail of the interventions and outcomes being studied or reporting was inconsistent, with key design and outcome details omitted. Moreover, in four of the five studies, patients were on multiple therapies alongside the trial drug, limiting the ability to discern whether a specific intervention was related to the outcome. Following a formal risk of bias assessment, four studies were rated as high risk of bias, and the fifth as moderate risk.

Tocilizumab

Four studies examining the clinical impact of tocilizumab in Covid-19 were identified; two retrospective case series and two case reports (Table 1). In a retrospective series from China, tocilizumab was administered to 21 patients with 81% severe and 19% critical (17 and 4 patients, respectively) Covid-19 [12]. Severe Covid-19 was defined as tachypnoea and/or respiratory failure, and critical Covid-19 included those requiring mechanical ventilation or organ support on ICU. Mean age of patients was 56.8 +/- 16.5 years, with a male majority of 85.7% (n=18). Mean IL-6 levels were elevated at 132.4 +/- 278.5 pg/mL. Together with standard of care, which included lopinavir and methylprednisolone, all patients received at least a single dose of intravenous tocilizumab 400mg, with three patients (14%) administered a second dose within 12 hours of the first due to fever.

Following tocilizumab, all patients rapidly improved with complete resolution of their fever within 24 hours (Table 2). Of the 19 patients whose oxygenation and blood results were

reported, there was a statistically significant improvement in oxygen saturations by day five post-treatment. 15 patients (79%) had reduced oxygen support; one no longer needed supplementary oxygen; two were extubated and one began the ventilator weaning process. Alongside clinical improvement mean CRP reduced from 75.1 +/- 66.8 mg/L to 2.72 +/- 3.6 mg/L on day 5 post tocilizumab. Radiological improvement in ground-glass opacities occurred in 91% (n=19). At the time of study publication, 19 patients (91%) had been discharged, and two (9%) remained in a stable condition in hospital. No adverse drug reactions to tocilizumab were reported.

In a further retrospective observational case series from China, treatment responses to tocilizumab were explored in 15 patients with Covid-19[14]. The median age of the included patients was 73 years (62-80); 75% were male. Baseline comorbidities included hypertension, diabetes and previous cerebrovascular accident in 60%, 27% and 20% respectively. Patients were stratified into moderately, seriously and critically ill based on national guidelines. All patients received an initial 80-600mg dose of tocilizumab either alone (47%) or in combination with methylprednisolone (53%). Five patients (33%) were administrated subsequent doses of tocilizumab.

At Day 7 post initial administration of tocilizumab, three patients (20%) had died, two (13%) had worsening of their disease, and the remaining 10 patients (67%) demonstrated clinical stability. A mild rise of 74.8 pg/mL (-0.8-175.6) in median IL-6 levels from pre-treatment values was seen in those with clinical stabilisation, whilst the five cases who died or worsened had a dramatic rise of 3581.2 pg/mL (591.9-4983.6). The median CRP value before

tocilizumab therapy was 126.9 mg/L (10.7-257.9) and dropped to 11.2 mg/L (0.02-113.7) after therapy ($p<0.01$). No adverse drug reactions to tocilizumab were reported.

In a case report from France, a 42-year-old male with renal cell carcinoma was hospitalised with fever and bone pains[15]. Following the development of a persistent cough, the patient tested positive for SARS-CoV-2 six days into hospital admission and was commenced on antiviral (lopinavir-ritonavir) therapy. On day eight the patient developed respiratory failure requiring supplemental oxygen, and was administered two doses, eight hours apart, of intravenous tocilizumab at 8mg/kg. Subsequently, he reported improved symptoms, and on day 12, he was afebrile, had discontinued supplemental oxygen therapy, had shown radiological improvement of ground-glass changes, and experienced a decrease in CRP from 225mg/L to 33mg/L.

In a case report from China, a 60-year-old male with a history of multiple myeloma was admitted with chest tightness and breathlessness after having tested positive for SARS-CoV-2 16 days previously[13]. On admission the patient was hypoxic and having been previously prescribed antibiotics and antivirals, the patient was administered with intravenous methylprednisolone for five days. On day nine, in view of ongoing severe symptoms, radiological ground-glass opacities, and elevated serum IL-6 levels, he was prescribed a single dose of IV Tocilizumab 8mg/kg. Within 72 hours, chest symptoms had resolved, and IL-6 levels gradually returned to normal over approximately ten days. After normalisation of IL-6 levels, a second peak was observed 48 hours later followed by a rapid decrease. Following a 26 day stay in hospital the patient was successfully discharged home.

Quantitative synthesis demonstrates that IL-6 was elevated prior to intervention with tocilizumab, and median difference seven days later demonstrated a further increase (Table 4). Distinguishing those who deteriorated from clinical stability or improvement indicates that IL-6 change was substantially greater where clinical outcome was poor (Figure 2). This feature was not observed when distinguishing clinical outcomes in CRP change, with variable decreases in CRP reported regardless of poor outcome. CRP levels decreased in all case series evaluated (Table 4).

Search of clinical trial registers identified 16 ongoing studies investigating the therapeutic role of tocilizumab in Covid-19[16-30] (Table 5). Of these studies, ten are based in Europe, four in China and two in the USA. Twelve of the studies are multi-centre randomised or observational clinical trials. Study sample sizes range from 38 to 400 with a cumulative sample size of 2568. Criteria for eligible participants vary across studies, with many specifying respiratory failure and/or elevated IL-6 as a prerequisite. The dose of tocilizumab administration is not entirely consistent across the studies with 8mg/kg the commonly studied dose. Other dose examples include 200mg and 324mg. The majority of studies (n=12) compare tocilizumab against usual care, whereas others compare tocilizumab against an alternate dose or with other agents considered to have a possible therapeutic role in Covid-19. Significant heterogeneity exists in the primary endpoints adopted by studies, including resolution of fever at 24 hours, clinical improvement at day 15, or in-hospital mortality.

Siltuximab

A single Italian retrospective case series was identified reporting preliminary data from an ongoing study from 21 Covid-19 patients with ARDS receiving siltuximab as part of a local compassionate-use programme[31] (Table 1). The median age was 64 years (48-75), with a male majority (86%). Baseline comorbidities included diabetes, hypertension and cardiovascular disease in 24%, 43% and 19% respectively. Serum CRP was raised in all patients (median 23.4 mg/dL; range 9.5-43.1 mg/dL), and IL-6 was elevated (median 139.5pg/mL; range 113-239 pg/mL) in 19 patients with available measurements (90%) (Table 2). All patients required ventilation with either non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP). Within 48 hours of initiating either CPAP or NIV, intravenous siltuximab was administered at a dose of 11mg/kg. A second dose within 48-72 of the first was administered in five patients (24%) at the discretion of the treating physician.

All patients were followed for at least seven days after administration of siltuximab. At the time of study analysis, seven (33%) had experienced an improvement and no longer required non-invasive ventilatory support, nine (43%) had no clinical change, and five (24%) died or clinically declined requiring intubation. In the 16 (76%) study patients with available CRP data at day five, all experienced a return to within the normal range. The stratification by clinical outcome of those with available CRP data was not reported by the authors, extracting estimated CRP levels plotted by the authors indicates a decline in mean CRP following intervention (Table 4).

Three ongoing clinical trials of siltuximab in Covid-19 were identified with a collective target sample size of 492 participants once complete (Table 6). The first is an Italian single-centre retrospective series of 50 patients with ARDS[32]. Siltuximab is being compared against usual care with an endpoint of mortality or need for invasive ventilation by day 30. The second is a Spanish single-centre randomised clinical trial (RCT) of 100 participants that is yet to commence recruitment[33]. Eligible patients will include those with progressive radiographic changes or respiratory failure. Siltuximab will be compared against methylprednisolone for preventing ICU admission. The third is a Belgian multi-centre RCT where siltuximab is being given alone or in combination with other immunomodulatory agents in patients with respiratory failure and signs of cytokine storm syndrome[16]. Recruitment has commenced and a six-category ordinal outcome scale measured at day 15 will be used as the endpoint.

Sarilumab

No published studies were identified for Sarilumab in Covid-19. Five ongoing multicentre studies have been identified based in Europe or USA[34-38] (Table 7). Four studies are RCTs and have commenced recruitment. Sample sizes range from 200 to 400 with a cumulative estimated sample size of 1390 once complete. Three studies necessitate respiratory failure in inclusion criteria; the remaining two are targeted towards those with multi-organ dysfunction. Sarilumab is being compared with either usual care or other immunomodulatory and antiviral agents. The majority of these studies specify an ordinal outcome scale as the endpoint, although the time points for these are not consistent across studies.

Anakinra

No published studies were identified for anakinra in Covid-19. Three multicentre studies with an estimated cumulative sample size of 416 patients are planned, and recruitment has commenced in two (Table 8)[16, 25, 39]. Evidence of cytokine storm syndrome is a consistent inclusion criterion for participation. However, primary endpoints differ across the studies, including a six-point ordinal outcome scale at day 15, proportion requiring mechanical ventilation at day 15, or detailed ICU scores at day eight. Alongside anakinra, patients may be randomised to a number of other antiviral or immunomodulatory agents.

Discussion

In this systematic review we demonstrate a plausible role for immunomodulatory agents in the treatment of Covid-19. Primary outcomes were inconsistently reported but suggest many patients experienced an improvement in status seven days following therapy. In one of two retrospective case series exploring the effects of tocilizumab, treatment was associated with rapid clinical, laboratory and radiological improvements. At the time of study publication, 91% of study participants had been discharged from hospital. In the second retrospective series, studying tocilizumab in an older population, 67% of patients improved and 33% either died or experienced deterioration. In the only identified study of siltuximab, treatment of those requiring non-invasive ventilatory support was associated with stability or improvement in 76% and death in 24%. No adverse events were identified, but in the absence of a control group, accurate determination of the harms of any

experimental drug can be impossible[40]. No suitable studies in SARS or MERS, or studies investigating sarilumab or anakinra in Covid-19 were found. Twenty-five registered clinical trials exploring immunomodulatory agents in Covid-19 were identified, of which the majority have commenced recruitment.

There is emerging evidence from non-interventional studies to suggest elevated IL-6 cytokine levels are significantly associated with adverse clinical outcomes in Covid-19 including ARDS and death[4], but it remains unclear whether IL-6 merely represents a biomarker of severity or whether it can be targeted for therapeutic interventions. Of the studies included in our review that measured serum IL-6, all reported elevated baseline levels. In the only case series measuring pre and post-tocilizumab IL-6 levels, there was an apparent distinction in the amount IL-6 continued to rise according to clinical outcomes, with those who responded to tocilizumab presenting the smallest IL-6 change. This discrepancy in effect was not observed using CRP levels within the same series.

The immunological mechanisms in Covid-19 are not fully elucidated, but evidence suggests an overly activated immune response characterised by the release of pro-inflammatory cytokines including IL-1 and IL-6, known as cytokine release syndrome (CRS) may play a vital role[3]. CRS, a recognised consequence of various other aetiologies including autoimmunity, malignancy and chimeric antigen receptor (CAR) T cell therapies, has been successfully managed with immunomodulatory therapies, raising the possibility of a similar role for immunomodulatory therapy in Covid-19 induced CRS[41].

The case fatality ratio (CFR) in patients with critical Covid-19 is estimated to be around 49%, although recorded mortality rates vary across countries[42]. In a report analysing outcomes from over 1500 patients with Covid-19 admitted to an ICU in the UK, mortality ranged from 19.4% to 66.3% depending on the level of respiratory support required[43]. All participants from included studies in our review had respiratory failure requiring at least basic respiratory support. In contrast to the mortality figures above, the CFR from the studies in this review was 6.8% (4/59; 3 Luo et al; 1 Gritti et al), but it must be acknowledged these case series data are subject to substantial bias. There may also be important differences in study participant characteristics, but the seemingly low CFR suggests immunomodulatory therapy is worth exploring further.

In this review we highlight multiple limitations and considerable sources of inter-study heterogeneity of both completed and ongoing studies. All included studies were individual case reports or non-randomised retrospective case series of relatively modest size, with a moderate or high risk of bias. Although the majority of studies necessitated respiratory failure, participant criteria were not entirely consistent across the studies. The dose of tocilizumab therapy included 8mg/kg, 400mg and 80-600mg across the studies, and patients were concurrently commenced on other agents including antivirals and steroids, resulting in challenges with demonstrating causality. Study outcomes were not uniform and a combination of clinical, laboratory and radiological outcomes were reported, rather than a single consistent endpoint.

Whilst many of the registered ongoing clinical trials are prospective studies of reasonable size with randomised interventions, they display similar inconsistency in participant and

intervention criteria with several diverse endpoints being studied. This may make future comparisons and pooling of results across clinical trials difficult. Studies of immunomodulatory therapies in Covid-19 should consider focusing on participants with evidence of a hyperinflammatory response, and outcomes should be standardised. A number of studies utilise an ordinal scale measured at day 15 focusing on relevant clinical outcomes such as death, ventilation and hospitalisation. Such patient-focused outcomes may be more important to patients than others such as resolution of fever at 24 hours, or time to normalisation of CRP.

This review has a number of strengths. Our search strategy was kept broad and included search of pre-print servers to ensure our screening for inclusion was as comprehensive as possible. We stipulated no restrictions on the type of studies to be included. No language restrictions were applied to enable inclusion of any early Chinese studies. Searches of clinical trial registries included clinicaltrials.gov, EU clinical registry and the Chinese clinical registry; again, ensuring our strategy was comprehensive. Covid-19 is a truly global pandemic; the data presented here represent findings from different countries, offering diversity in ethnic background which should be built upon in further study and analysis.

Despite employing a highly sensitive search strategy, this review has important limitations, particularly relating to the methodological quality of the included studies. As all studies focused on patients with respiratory failure, these findings cannot be extrapolated to Covid-19 participants without evidence of respiratory failure. All retrieved studies were retrospective in nature with a moderate or high risk of bias, and therefore findings need to be reproduced in well-conducted prospective clinical trials before immunomodulatory

therapy can be recommended for clinical use. Ongoing and future trials, such as those summarised here, should ensure baseline and follow up data is complete for all primary and secondary endpoints, facilitating quantitative synthesis across studies.

In summary, we demonstrate serum IL-6 levels appear to be elevated in patients with severe Covid-19 and changes in response to tocilizumab may distinguish disease outcomes. Preliminary studies suggest inhibition of IL-6 may be effective in managing the assumed hyperinflammatory response associated with severe Covid-19. These early data justify the need for ongoing well-designed randomised clinical studies with concurrent control groups to explore this hypothesis further.

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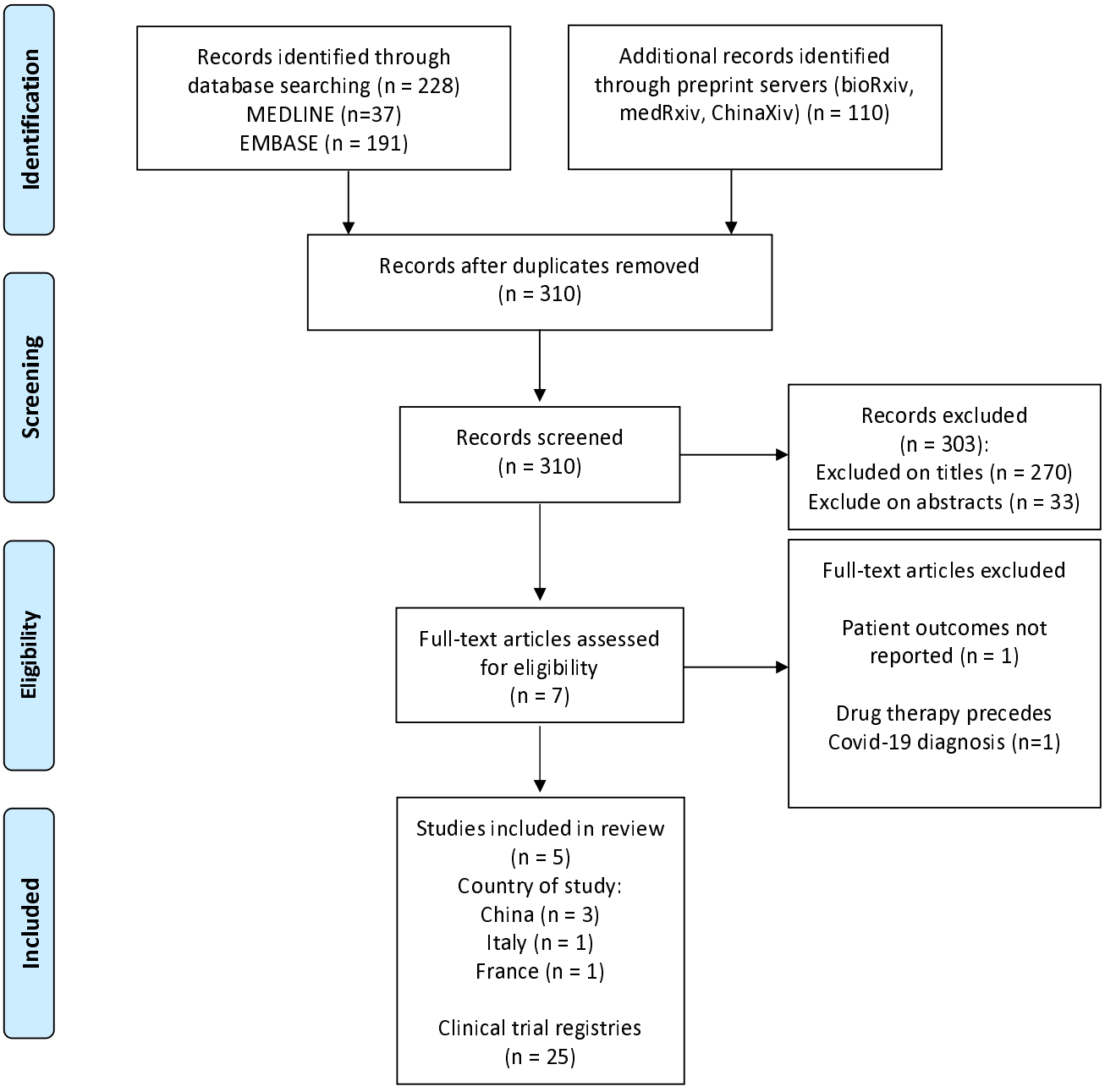

Fig 1 Flow diagram illustrates systematic search and screening strategy, including numbers meeting eligibility criteria and numbers excluded.

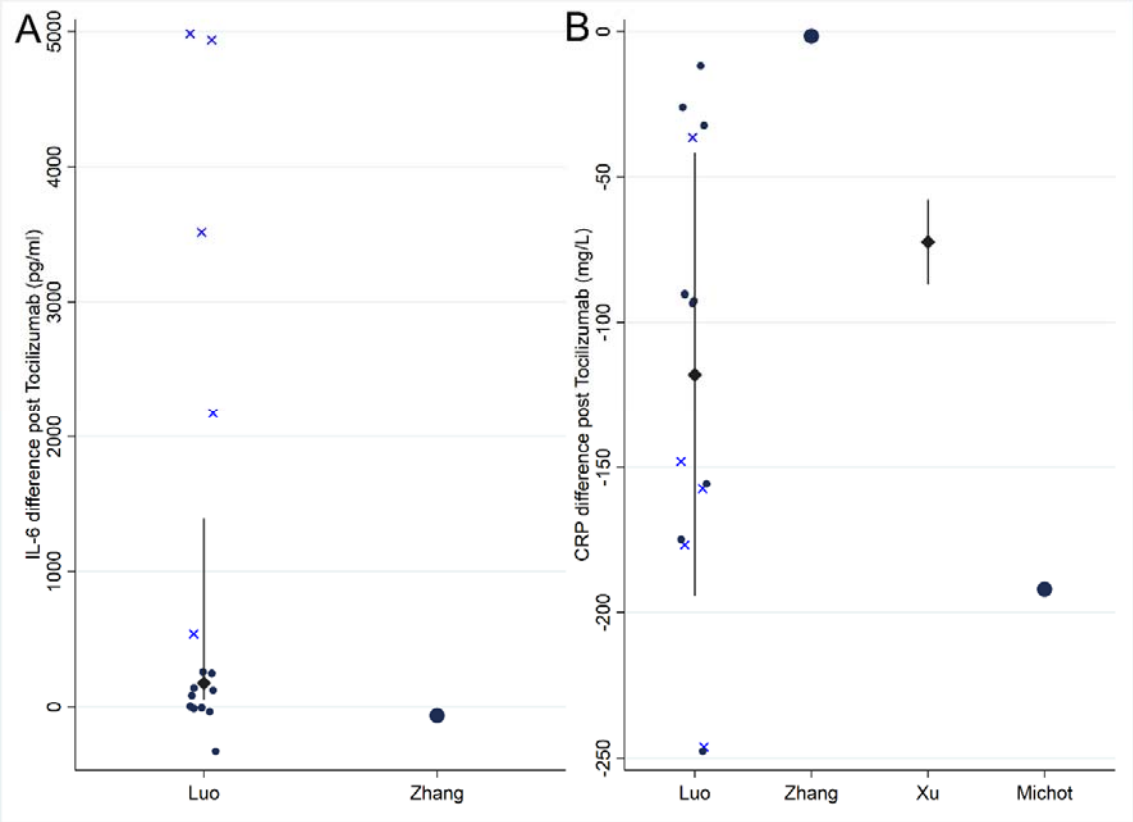

Fig 2 Summary biomarker data as reported in Luo et al 2020; Zhang et al 2020; Xu et al 2020; Michot et al 2020. A. Diamond and error represents median difference in IL-6 (pg/ml) post Tocilizumab, with interquartile range. B. Diamond and error represents mean difference in CRP (mg/L) post Tocilizumab, with standard deviation in B. Small circles represent individual data points within case series for people who showed clinical stability or improvement, small crosses represent individual data points within case series for people who clinically deteriorated or died, large circles are individual data points from case studies.

Table 1 – Methodological and patient characteristics of included studies

Author, year	Therapy	Study design	Country of study	Centre	Study size	Follow-up, days (median)	Age	Sex (male)	Diabetes	Hypertension	Participant criteria	Outcomes reported
Xu et al 2020	Tocilizumab	Retrospective case series	China	Single centre	21	N/R	56.8 (16.5)	85.7%	23.8%	42.8%	Severe - tachypnoea and/or respiratory failure Critical - mechanical ventilation or organ support on ICU	Hospital status; Ventilatory requirement; Imaging; CRP; Lymphocyte
Luo et al 2020	Tocilizumab	Retrospective case series	China	Single centre	15	7	73 (62-80) Median (range)	75%	27%	60%	Moderately, severely or critically ill (not otherwise specified)	Mortality status; IL-6; CRP
Gritti et al 2020	Siltuximab	Retrospective case series	Italy	Single centre	21	8	64 (48-75) Median (range)	85.7%	23.8%	42.8%	Requiring non-invasive ventilatory support (NIV or CPAP)	Mortality status; Ventilatory requirement; CRP
Zhang et al 2020	Tocilizumab	Case report	China	Single centre	1	42	60	100% (CR)	0	0	Respiratory failure	Time to discharge; IL-6; Imaging
Michot et al 2020	Tocilizumab	Case report	France	Single centre	1	15	42	100% (CR)	0	0	Respiratory failure	Mortality status; Oxygenation; CRP; Temperature; Imaging

CPAP, continuous positive airways pressure; CR, case report; CRP, C reactive protein; ICU, intensive care unit; IL6, interleukin 6; NIV, non-invasive ventilation

Table 2 – Results from included studies

Author and year of publication	Dose	Other Therapies	Outcomes	Drug adverse events
Xu et al 2020	IV Tocilizumab 400mg; 20% administered second dose within 12 hours due to fever	Lopinavir and Methylprednisolone	All had resolution of fever within 24 hours; 75% had reduced oxygen support; CRP and lymphocytes returned to normal in 84% and 53% respectively. 91% had radiological improvement; 91% discharged; 9% remain stable	Nil
Luo et al 2020	Tocilizumab 80-600mg. 33% administered subsequent doses	53% given Methylprednisolone	20% died; 13% had worsening of disease; 67% demonstrated clinical stability; median CRP fell from 126.9 to 11.2 mg/L. Drop in IL-6 in 67%	Nil
Gritti et al 2020	IV Siltuximab 11mg/kg; 24% had a second dose within 48-72 hours	Usual care	33% improved; 43% stable; 24% worsened or died	Cerebrovascular accident – related to therapy?
Zhang et al 2020	IV Tocilizumab 8mg/kg; two doses	Lopinavir-Ritonavir	By Day 4 – Resolution of fever; discontinuation of supplemental oxygen therapy; radiological improvement in ground glass changes; CRP dropped from 225mg/L to 33mg/L	Nil
Michot et al 2020	IV Tocilizumab 8mg/kg	IV Methylprednisolone for 5 days	At 72 hours – Resolution of chest symptoms; IL-6 levels returned to normal	Nil

Table 3. Primary clinical outcomes

Author	Cohort	Therapy	Treated N	Hospitalised days post treatment	Outcome score	Outcome recorded	1: death	2: supported	3: recovery	4: discharge
Luo et al 2020	series	Tocilizumab	15	not reported	3 (2 - 3)	day 7	3	2	10	0
Xu et al 2020	series	Tocilizumab	21	13.5 (3.1)	4 (4 - 4)	not reported	0	1	1	19
Gritti et al 2020*	series	Siltuximab	21	not reported	2 (2 - 3)	day 7	1	13	7	0
Zhang et al 2020	case	Tocilizumab	1	17	4	day 10	0	0	0	1
Michot et al 2020	case	Tocilizumab	1	not reported	3	day 7	0	0	1	0

Hospitalised days post treatment reported as mean (standard deviation) for series and absolute days in cases. Outcome score presented as median (interquartile range) for series or absolute score in cases: using adapted ordinal outcome score where 1 indicates death, 2 describes hospitalised patients requiring ventilatory support (IMV/ECMO/NIV/CPAP), 3 describes hospitalised and clinically stable patients in recovery, 4 describes discharged patients. Outcome recorded presented as days following named therapy.

Table 4. CRP and IL-6 reported outcomes

Series	Therapy	N Treat	CRP pre	CRP post	CRP change	CRP follow up	IL-6 pre	IL-6 post	IL-6 change	IL-6 follow up
Luo et al 2020	Tocilizumab	15	131.8 (77.4)	13.8 (25.6)	-118.0 (76.3)	7 (4 - 7)	46.8 (28.2 - 75.2)	249.0 (152.6 - 1467.4)	175.5 (51.4 - 1394.6)	7 (3 - 7)
Xu et al 2020	Tocilizumab	21	75.1 (66.8)	2.72 (3.6)	-72.3 (14.6)	5 (5 - 5)	not reported	not reported	not reported	-
Gritti et al 2020*	Siltuximab	21	213.8 (90.7)	70.5 (100.4)	-143.3 (115.3)	7 (2 - 7)	139.5 (113-239)	not reported	not reported	-

Pre intervention levels, post, and change in c-reactive protein (CRP) presented as mean (standard deviation) in mg/L and median days follow up (range). Interleukin-6 (IL-6) presented as median (interquartile range) in pg/L. *CRP values estimated from Gritti et al 2020 Figure 1.

Table 5 – Registered tocilizumab clinical trials in Covid-19

Study	*Status*	*Country*	*Design*	*Sample size*	*Participants*	*Intervention*	*Comparator*	*Primary outcome*
NCT04330638	Recruiting	Belgium	Multi-centre RCT	342	Covid-19 with respiratory failure and signs of cytokine release syndrome	Tocilizumab or Anakinra + Tocilizumab or Anakinra + Siltuximab or Siltuximab or Anakinra	Usual care	Clinical improvement at Day 15 according to a six-category ordinal scale
NCT04331795	Recruiting	USA	Single-centre non-randomised intervention	50	Covid-19 with fever and radiographic infiltrates	Tocilizumab 200mg in those with risk factors for decompensation	Tocilizumab low dose (80mg) in those without risk factors for decompensation	Fever at 24 hours; Time to CRP normalisation (hours)
NCT04332094	Recruiting	Spain	Multi-centre RCT	276	Covid-19 with fever and radiographic infiltrates	Tocilizumab 324mg s/c + further 324mg s/c at 12 hours; Hydroxychloroquine; Azithromycin	Hydroxychloroquine; Azithromycin	In hospital mortality Need for mechanical ventilation in the ICU
NCT04320615	Recruiting	USA	Multi-centre RCT	330	Covid-19 with respiratory failure	IV Tocilizumab 8mg/kg + one further dose if no improvement	Placebo	Clinical improvement at Day 15 according to a seven-point ordinal scale
NCT04332913	Not yet recruiting	Italy	Single-centre Observational	30	Covid-19 with ARDS and signs of cytokine release syndrome	Tocilizumab	Usual care	Percentage of patients with complete recovery (afebrile and normal oxygenation) at Day 14
NCT04335305	Not yet recruiting	Spain	Multi-centre RCT	24	Covid-19 with respiratory failure	Tocilizumab 8mg/kg + Pembrolizumab	Usual care	Percentage of patients with normalisation of oxygenation at Day 14
NCT04335071	Not yet recruiting	Switzerland	Multi-centre RCT	100	Covid-19 with respiratory failure	Tocilizumab 8mg/kg repeated once if no improvement	Usual care	No. of patients with ICU admission (Day 7), No. of patients with intubation (Day 14), No of patients with death (Day 28)

NCT04317092	Recruiting	Italy	Multi-centre observational	400	Covid-19 with respiratory failure	Tocilizumab 8mg/kg	Usual care	One-month mortality rate
NCT04310228	Recruiting	China	Multi-centre RCT	150	Covid-19 with elevated Interleukin-6	Favipiravir + tocilizumab	Tocilizumab 400mg + one further dose if fever; Favipiravir	Clinical cure rate at 3 months (time to negative viral load, lung image improvement, resolution of fever)
NCT04339712	Not yet recruiting	Greece	Multi-centre nonrandomised intervention	20	Covid-19 with cytokine storm syndrome	Tocilizumab 8mg/kg or Anakinra 200mg TDS if tocilizumab CI	Usual care	Decrease of SOFA score; Improvement of lung involvement measurements; Increase of pO2/FiO2 (Day 8)
NCT04306705	Recruiting	China	Single-centre Retrospective cohort	120	Covid-19, radiographic or clinical improvement of lung involvement and IL-6 > 3 times normal	Tocilizumab 8mg/kg	Usual care; Continuous Renal Replacement Therapy	Percentage of patients with complete recovery (afebrile and normal oxygenation) at Day 14
NCT04315480	Not yet recruiting	Italy	Single-centre RCT	38	Covid-19 with multifocal interstitial pneumonia and respiratory failure	IV Tocilizumab 8mg/kg	Usual care	Improvement of oxygenation at Day 7
NCT04331808	Not yet recruiting	France	Multi-centre RCT	240	Covid-19 with respiratory failure	Tocilizumab 8mg/kg + second injection at Day 3 if no response	Usual care	Tracheal extubation (Day 14), WHO progression scale (Day 4)
ChiCTR2000029765	Recruiting	China	Multi-centre RCT	188	Covid-19 with elevated Interleukin-6	Tocilizumab	Usual care	Cure rate
ChiCTR2000030196	Not yet recruiting	China	Multi-centre nonrandomised intervention	60	Covid-19 with cytokine storm syndrome and elevated IL-6	Tocilizumab	Usual care	Resolution of cytokine release syndrome

Table 6. Registered siltuximab clinical trials in Covid-19

Study ID	Status	Country	Design	Sample size	Participants	Intervention	Comparator	Primary outcome
NCT04322188	Recruiting	Italy	Single-centre retrospective cohort	50	Confirmed Covid-19 with ARDS	Siltuximab	Usual care	Need for invasive ventilation or 30-day mortality
NCT04329650	Not yet recruiting	Spain	Single-centre RCT	100	Covid-19 with radiographic changes with respiratory failure	Siltuximab 11mg/kg	Methylprednisolone	ICU admission
NCT04330638	Recruiting	Belgium	Multi-centre RCT	342	Confirmed Covid-19 with respiratory failure and signs of cytokine release syndrome	Tocilizumab or Anakinra + Tocilizumab or Anakinra + Siltuximab or Siltuximab or Anakinra	Usual care	Time to clinical improvement at Day 15 according to a six-category ordinal scale

Table 7. Registered sarilumab clinical trials in Covid-19

Study ID	Status	Country	Design	Sample size	Participants	Intervention	Comparator	Primary outcome
NCT04327388	Recruiting	Multinational	Multi-centre RCT	300	Covid-19 with multi-system organ dysfunction or immunocompromised at baseline	Sarilumab	Placebo	Resolution of fever, 7-point ordinal scale
NCT04322773	Recruiting	Denmark	Multi-centre RCT	200	Covid-19 and respiratory failure	Tocilizumab 400mg IV **or** Tocilizumab 162mg SC **or** Sarilumab 200mg SC	Usual Care	Time to independence from supplementary oxygen therapy (days)
NCT04315298	Recruiting	USA	Multi-centre RCT	400	Covid-19 with multi-system organ dysfunction or immunocompromised at baseline	Sarilumab high dose or Sarilumab low dose	Placebo	Change in CRP levels at day 4, 7-point ordinal scale at day 29
NCT04324073	Recruiting	France	Multi-centre RCT	240	Covid-19 and respiratory failure	Sarilumab	Usual Care	Survival at day 14, Progression scale at day 4, tracheal extubation at day 14
NCT04321993	Not yet recruiting	Canada	Multi-centre nonrandomised intervention	250 (assumed)	Covid-19 with fever and respiratory failure	Sarilumab 200mg S/C, Lopinavir/ritonavir **or** hydroxychloroquine **or** Baricitinib	Usual Care	Clinical status at day 15 (on a 7-point ordinal scale)

Table 8. Registered anakinra clinical trials in Covid-19

Study ID	Status	Country	Design	Sample size	Participants	Intervention	Comparator	Primary outcome
NCT04330638	Recruiting	Belgium	Multi-centre RCT	342	Covid-19 with respiratory failure and signs of cytokine release syndrome	Tocilizumab or Anakinra + Tocilizumab or Anakinra + Siltuximab or Siltuximab or Anakinra	Usual care	Time to clinical improvement at Day 15 according to a six-category ordinal scale
NCT04324021	Recruiting	Italy	Multi-centre RCT	54	Covid19 with respiratory failure and presence of hyperinflammation	Emapalumab or Anakinra	Usual care	Invasive mechanical ventilation or ECMO at day 15
NCT04339712	Not yet Recruiting	Greece	Multi-centre nonrandomised intervention	20	Covid-19 with cytokine storm syndrome	Tocilizumab 8mg/kg or Anakinra 200mg TDS if tocilizumab CI	Usual care	Decrease of SOFA score; Improvement of lung involvement measurements; Increase of pO2/FiO2 (Day 8)

Table 9. Risk of bias assessment

Author and year of publication	Selection	Ascertainment	Causality	Reporting	Overall risk of bias assessment
Xu et al 2020	Moderate	Moderate	High	High	High
Luo et al 2020	Moderate	High	High	High	High
Gritti et al 2020	Low	Moderate	Low	Moderate	Moderate
Zhang et al 2020	N/A	Low	High	Moderate	High
Michot et al 2020	N/A	Low	High	Moderate	High

Appendix

1. Respiratory Distress Syndrome, Adult/

2. SARS Virus/

3. Severe Acute Respiratory Syndrome/

4. severe acute respiratory distress syndrome*.mp.

5. Coronavirus Infections/

6. Coronavirus/

7. coronav*.mp.

8. covid*.mp.

9. SARS.mp.

10. Middle East Respiratory Syndrome Coronavirus/

11. MERS.mp.

12. anakinra.mp.

13. kineret.mp.

14. tocilizumab.mp.

15. altizumab.mp.

16. actemra.mp.

17. roactemra.mp.

18. sarilumab.mp.

19. kevzara.mp.

20. siltuximab.mp.

21. sylvant.mp.

22. Interleukin 1 Receptor Antagonist Protein/

23. anti-IL6.mp.

24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

25. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

26. 24 and 25

MEDLINE search strategy (last carried out on 8th April 2020)