**Online Supplementary Material to:**

**Rationale and Evidence on the use of Tocilizumab in COVID-19:**

**A Systematic Review**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Recruiting status | Study design | Country  |  Population (n patients)  | Intervention Group § | Comparison Group(s)  | Primary Outcomes  |
| NCT04310228 / ChiCTR2000030894 | Recruiting | Multicentre RCT | China | Patients with COVID-19 and high IL-6 (n=150) | Combination group (Favipiravir + Tocilizumab)Favipiravir: oral 1600mg BID on the day1; from the day 2 to day 7, 600mg BID;Tocilizumab: e.v. first dose of 4 ~ 8mg/kg (recommended dose 400mg).Additional application (the same dose as before) is still febrile within 24 hours, with ≥ 12 hours interval between two doses. | Favipiravir group: oral 1600mg BID on day 1; from day 2 to day 7, 600mg BID;Tocilizumab groupe.v. first dose of 4 ~ 8mg/kg (recommended dose 400mg).Additional application (the same dose as before) is still febrile within 24 hours, with ≥ 12 hours interval between two doses. | Clinical cure rate |
| ChiCTR2000029765 | Recruiting | Multicentre RCT | China | Patients with COVID-19 pneumonia and high IL-6 (n=188) | Tocilizumab | Conventional therapy | Clinical cure rate |
| NCT04315480 | Active, not recruiting | Single-centre Simon's Two-stages Optimal Design Trial | Italy | Patients with COVID-19 (n=38) | Tocilizumab i.v 8 mg/kg single administration | All the patients enrolled are treated with tocilizumab | Arrest in deterioration of pulmonary function or improving in pulmonary function at day 7  |
| NCT04306705 | Recruiting | Multicentre retrospective cohort study | China | Patients with COVID-19 (n=120) |  Tocilizumab i.v. 8 mg/kg | Continuous Renal Replacement Therapy | Normalization of Fever and Oxygen Saturation at day 14 |
| NCT04335071 | Recruiting | Multicentre RCT | Switzerland | Patients with COVID-19 (n=100) | Tocilizumab i.v. 8 mg/kg single administration (up to a maximum of 800mg per dose). Second dose if no clinical improvement. | Placebo | ICU admission at day 7, intubation at day 14, mortality at day 28 |
| NCT04345445 | Not yet recruiting | Single centre crossover randomized trial | Malaysia | Patients with COVID-19 (n=310) | Tocilizumab i.v. 8 mg/kg single administration | Methylprednisolone i.v. 120mg/day for 3 days | Need of mechanical ventilation and mean days of ventilation through study completion and at 6 months |
| NCT04333914 | Recruiting | Multicentre RCT | France | COVID-19 pneumonia and advanced or metastatic hematological or solid tumor(273) | Tocilizumab (Only if moderate-severe)400 mg i.v intravenously, single infusion at Day 1. | Chloroquine analogue (GNS651)If mild/asymptomatic: 200mg bid loading dose for 2 days then, 200 qd orally for 14 consecutive days.If moderate-severe :200mg bid loading dose for 2 days then, 200 qd/day orally, per os, for 14 consecutive days.Nivolumab:Only if mild/asymptomatic: 0.3mg/Kg, intravenously, single infusion at Day 1.Standard of care group:Conventional therapy | Survival rate at day 28 |
| NCT04332094 | Recruiting | Multicentre RCT | Spain | COVID-19 pneumonia(n=276) | Tocilizumab162 mg sc x 2 doses + tocilizumab 162mg sc x 2 doses at 12 hours (day 1)Drug: Hydroxychloroquine400 mg / 12h v.o. day 1 followed by 200 mg / 12h v.o. for 6 days (7 days in total)Azithromycin oral 500 mg / day for 3 days | Hydroxychloroquine oral400 mg / 12h day 1 followed by 200 mg / 12h v.o. for 6 days (7 days in total)Azithromycin oral 500 mg / day v.o. for 3 days | In-hospital mortality and need for mechanical ventilation in the Intensive Care Unit at day 14 and at dimission |
| NCT04330638 | Recruiting | Multicentre RCT | Belgium | Patients with COVID-19 (n=342) | Anakinra-Tocilizumab group:Anakinra s.c 100 mg/day for 28 days or until hospital dischargeTocilizumab e.v. 8 mg/kg (up to a maximum of 800mg per dose), single administrationTocilizumab group:Tocilizumab e.v. 8 mg/kg (up to a maximum of 800mg per dose), single administration | Anakinra-Siltuximab group:Anakinra s.c 100 mg/day for 28 days or until hospital dischargeSiltuximab e.v. 11 mg/kg, single administrationSiltuximab group:Siltuximab e.v. 11 mg/kg, single administrationAnakinra group:Anakinra s.c 100 mg/day for 28 days or until hospital dischargeUsual Care group:Conventional therapy | Time to clinical Improvement |
| NCT04332913 | Recruiting | Single centre prospective observational clinical study | Italy | Hospitalized patients with COVID-19 with high level of IL-6(n=30) | Tocilizumab | NA | Fever disappearance and return to normal SpO2 at day 14  |
| NCT04339712 | Recruiting  | Multicentre non-randomized clinical trial | Greece | Patients with COVID-19 with MAS or immune dysregulation(n=40) | TocilizumabIf immune dysregulation: tocilizumab i.v. 8mg/kg (up to a maximum of 800mg) single administration.  | If MAS: anakinra i.v. 200mg TID for 7 days. ( if kidney disfunction 100mg TID for 15 days) | Change of SOFA score, improvement of lung involvement and increase of pO2/FiO2 ratio at day 8 |
| NCT04335305 | Recruiting  | Multicentre RCT | Spain | Patients with COVID-19 and hyperinflammatory status (n=24) | Tocilizumab 8 mg/kg i.v. (up to 800 mg per dose) over 60 minutes single dose Plus Pembrolizumab (MK3475) 200 mg i.v. over 30 minutes single dose.Additional same dose of TCZ if no improvement in 12h. If SpO2 ≤ 94% on room air additional dose of pembrolizumab (MK-3475) after 3 weeks and/or an additional dose of tocilizumab after 4 weeks at physician's discretion | Standard care | Percentage of patients with normalization of SpO2 ≥96% at day 14 |
| NCT04346355 | Recruiting  | Multicentre RCT | Italy | Patients with COVID-19 (n=398) | Tocilizumab within 8 hours from entering the study 8 mg/kg i.v. (up to 800 mg) with repetition after 12 hours in case of worsening | Standard care.In case of worsening, TCZ 8 mg/kg i.v. (up to 800 mg) with repetition of the same dosage after 12 hours | ICU admission with invasive mechanical ventilation or death from any cause or clinical worsening at day 14 |
| NCT04320615 | Active, not recruiting | Multicentre RCT | USA, Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK | Patients with COVID-19 (n=450) | TCZ i.v. 8 mg/kg (up to 800 mg). Up to 1 additional dose if clinical worsening or no improvement | Placebo | Clinical Status Assessed Using a 7-Category Ordinal Scale at day 28 |
| NCT04331808 | Active, not recruiting | Single-centre RCT | France | Patients with COVID-19 (n=228) | Tocilizumab 8mg/kg at day 1 and if no response second injection at day 3 | Standard care | Survival without needs of ventilator utilization at day 14, WHO progression scale <=5 at day 4, cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14, decrease of WHO score of at least 1 point at day 4 |
| NCT04347031 | Active, not recruiting | Single-centre randomized trial | Russian Federation | COVID-19 pneumonia (n=320) | Combination: Hydroxychloroquine + azithromycin + Tocilizumab (dosage NA)Day 1: 800 mg of HCQ (2 tablets 200 mg X 2)Day 2 to 7: 400 mg of HCQ (1 tablet 200 mg X 2) per day Combination: Mefloquine + azithromycin + Tocilizumab (dosage NA)Day 1: 750 mg of mefloquine per day, (tablet 250 mg X 3)* Day 2: 500 mg of mefloquine, (tablets 250 mg X 2)
* Day 3 to 7: 250 mg of mefloquine
 | HydroxychloroquineDay 1: 800 mg of HCQ (2 tablets 200 mg X 2)Day 2 to 7: 400 mg of HCQ (1 tablet 200 mg X 2) per day Mefloquine Day 1: 750 mg of mefloquine per day, (tablet 250 mg X 3)* Day 2: 500 mg of mefloquine, (tablets 250 mg X 2)

Day 3 to 7: 250 mg of mefloquine. | Respiratory failure requiring ICU care at 3 months; clinical recovery at 3 months; mortality at 3 months |
| ChiCTR2000030196 | Not yet recruiting | Multicentre single-arm clinical trial | China | COVID-19 pneumonia with high IL-6 (n=60) | Tocilizumab | All the patients enrolled are treated with tocilizumab | Relieve of cytokine release syndrome |
| NCT04349410 | Enrolling by invitation | Single-centre RCT | USA | Patients with COVID-19(n=500) | Tocilizumab 8mg/kg IV (up to 800 mg). If no clinical improvement, three additional doses at q 8-hour intervals, for a total of 4-doses maximum.Any patient demonstrating cytokine release syndrome will automatically receive this treatment arm. | Active comparators.Drug: Hydroxychloroquine (200mg X3/die per 10 days) + Azithromycin (500mg i.v. day1, then 250mg i.v. days 2 to 5).Drug: Hydroxychloroquine (200mg X3/die per 10 days)+ Doxycycline (100mg i.v.X2)Drug: Hydroxychloroquine(200mg X3/die per 10 days)+ Clindamycin(p.o. 150-450mgX4 or 4800mg i.v./day for 7 days)Drug: Hydroxychloroquine(200mg X3/die per 10 days)+ Clindamycin(p.o. 150-450mgX4 or 4800mg i.v./day for 7 days) + Primaquine (200mg day1)Drug: Hydroxychloroquine (800mg + 400mg after 8h, then 400mg day 2 and day3), Clindamycin(p.o. 150-450mgX4 or 4800mg i.v./day for 7 days)+ Primaquine(200mg day1)Drug: Remdesivir (200 mg i.v. day 1, then 100 mg/day for 10days)Drug: Methylprednisolone (80 mg i.v. X2 per 7days)Drug: Interferon-Alpha2B X2Drug: Losartan (25mg/die)Drug: Convalescent Serum drom COVID-19 survivors | Improvement in FMTVDM (The Fleming Method for Tissue and Vascular Differentiation and Metabolism ) measurement with nuclear imaging at 72h |
| NCT04346693 | Active, not recruiting | Single-centre randomized trial | Russia | Hospitalized patients with COVID-19(n=320) | Hydroxychloroquine + azithromycin + / - tocilizumab + dalarginHCQ 400 mg twice per day for 1-2 days then 200 mg twice daily per six days.TCZ 400 mg i.v.; if insufficient effect, administration is repeated after 12h (simultaneously no more than 800 mg)AZ 500mg on day 1, then 250mg/day for the next four daysDalargin 10 mg i.v. daily symptoms remission And/ori.m injection of Dalargin 1 mg/day for 10 days | Hydroxychloroquine + azithromycin + / - tocilizumab + dalarginHCQ 400 mg twice per day for 1-2 days then 200 mg twice daily per six days.TCZ 400 mg i.v.; if insufficient effect, administration is repeated after 12h (simultaneously no more than 800 mg)AZ 500mg on day 1, then 250mg/day for the next four daysDalargin 10 mg i.v. daily symptoms remission And/ori.m injection of Dalargin 1 mg/day for 10 days | Change of PCR viral load at day0, after 96 hours and at day10; ARDS at day 10; Hospitalization at day 10;Mortality at day 30 and day 90; Clinical status at day 10 |
| NCT02735707 | Recruiting | Multicentre RCT | Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK | ICU patients with suspected CAP or COVID-19(n=7100) | Tocilizumab single 8 mg/kg i.v. (up to 800mg). | No intervention orDrug: Hydrocortisone50mg i.v. every 6 hours for up to 7 days or while the patient is in septic shock; or 100mg every 6 hours for up to 7 days.Drug: CeftriaxoneDrug: Moxifloxacin or LevofloxacinDrug: Piperacillin-tazobactamDrug: CeftarolineDrug: Amoxicillin-clavulanateDrug: Macrolide administered for 3-5 daysDrug: Macrolide administered for up to 14 days (Duration and dose of antibiotics determined by the treating clinician and local practice)Drug: Five-days oseltamivirDrug: Ten-days oseltamivir enterally twice daily for 5 days or until hospital discharge.Drug: Lopinavir/ritonavir 400/100mg enterally, or 5ml 80/20mg per mL solution suspension via gastric tube, every 12 hours for a minimum of 5 daysDrug: Hydroxychloroquine 800mg administered enterally every 6 hours until 2 doses, then 400mg every 12 hours for 12 doses or ICU discharge.Drug: Hydroxychloroquine + lopinavir/ritonavir (same dosage as above)Drug: Interferon-β1a once daily for 6 days or until ICU discharge;Anakinra 300mg as a bolus followed by maintenance doses of 100mg every 6 hours.Drug: Sarilumab single dose of 400mg | All-cause mortality at day 90;Days alive and outside of ICU at day 21 |
| NCT04374539 | Recruiting | Multicentre open label RCT | Spain | Patients with COVID-19 admitted in ICU with invasive mechanical ventilation(n=116) | Plasma exchanges with 5% human albumin and fresh frozen plasma in patients with quick <50% or only with 5% albumin in patients with quick of 50% or more. Polyclonal immunoglobulin at a dose of 100 mg / kg ev after each plasma exchange.AndKaletra: lopinavir/ritonavir: 2c/12h 7 days* Hydroxychloroquine sulfate 400 mg/12h the first day followed by 200 mg /12h for 4 days
* Azithromycin 500 mg first day, followed by 250 mg /d 4 days (oral or EV)
* Tocilizumab 400 mg (weight <75Kg) or 600 mg (weight ≥ 75 Kg)
* Methylprednisolone 250 mg EV three days and 30 mg/d another 3 days
* Anakinra 200mg/ 12h first day, 200mg / 24h two more days
* Clexane 40-60 mg/d
 | lopinavir/ritonavir: 2c/12h 7 days* Hydroxychloroquine sulfate 400 mg/12h the first day followed by 200 mg /12h for 4 days
* Azithromycin 500 mg first day, followed by 250 mg /d 4 days (oral or EV)
* Tocilizumab 400 mg (weight <75Kg) or 600 mg (weight ≥ 75 Kg)
* Methylprednisolone 250 mg EV three days and 30 mg/d another 3 days
* Anakinra 200mg/ 12h first day, 200mg / 24h two more days
* Clexane 40-60 mg/d
 | Mortality at day 28 |
| NCT04380818 | Recruiting | Multicentre nonrandomized clinical trial  | Spain | Moderate to severe COVID-19 with high IL6, PCR or D-dimer (n=106) | Radiation: Low-dose radiotherapyDrug: Hydroxychloroquine Sulfate200 mg/12h for 5 daysDrug: Ritonavir/lopinavir400/100 mg/12h for 7-10 daysDrug: Tocilizumab600 mg/day for 1-2 dosesDrug: Azithromycin500 mg/24h for 3 daysDrug: Corticosteroid (methylprednisolone/dexamethasone/prednisone)Drug: Low molecular weight heparinDevice: Oxygen supply | Drug: Hydroxychloroquine Sulfate200 mg/12h for 5 daysDrug: Ritonavir/lopinavir400/100 mg/12h for 7-10 daysDrug: Tocilizumab 600 mg/day for 1-2 dosesDrug: Azithromycin500 mg/24h for 3 daysDrug: Corticosteroid (methylprednisolone/dexamethasone/prednisone)Drug: Low molecular weight heparinDevice: Oxygen supplyOxygen | Change in P/F at day 2.In cases of impossibility the SaFiO2 will be determined |
| NCT04381936 | Recruiting | Multicentre RCT | UK | Hospitalized patients with suspected or confirmed COVID-19(n=12000) | Eligible patients will be randomly allocated between the available 5 treatment arms:TocilizumabOr AzithromycinOr Lopinavir-RitonavirOr HydroxychloroquineOr dexamethasone (in pregnancy or breastfeeding women, prednisolone)Simultaneously, eligible patients will be randomly allocated between convalescent plasma or no additional treatment.Convalescent plasmaSingle unit of ABO compatible (275mls +/- 75 mls) per day on day 1 and day 2 | One of the five treatment arm without plasma. | All-cause mortality at day 28 |
| NCT04322773 | Recruiting | Multicentre open-Label, Sequential and Cluster Randomized Trial | Denmark | Patients with confirmed COVID-19, oxygen therapy(n=200) | Tocilizumab ivsingle dose 400 mg intravenouslyOr 2 x 162 mg subcutaneously | Sarilumab 1 x 200 mg subcutaneously or standard care | Time to independence from supplementary oxygen therapy |
| NCT04361552 | Recruiting | Single-centre open-Labeled, Randomized Trial | USA | Hospitalized patients with covid-19(n=180) | Tocilizumab i.v | Standard care | Length of invasive mechanical ventilation (MV) |
| NCT04403685 | Recruiting | Multi-centre Randomized Clinical Trial | Brasil | Hospitalized patients with COVID-19 under oxygen therapy or MV and high inflammatory markers(n=150) | TocilizumabSingle-dose infusion of 8 mg/kg. Maximum dose of 800 mg. | Standard care | Clinical status at day 15 |
| NCT04361032 | Not yet recruiting | Multicentre, Comparative, Randomized Study | Tunisia | ICU patients with confirmed COVID-19(n=260) | Tocilizumab (LOC) (8mg/ kg per day) (1 injection per infusion). Only on the day1 | Deferoxamine 500 mg i.v. | Mortality rate at day 90 |
| NCT04377503 | Not yet recruiting | Single-centre prospective randomized controlled study | Brasil | Patients with confirmed COVID-19 and high IL-6 or inflammatory markers(n=40) | Tocilizumab 8 mg/kg. The dose will be repeated after 12 hours. | Methylprednisolone 1.5 mg / kg / day divided into 2 daily doses for 7 days, then 1 mg / kg / day for another 7 days. Finally 0.5 mg / kg / day until 21 days of use | Patient clinical status at day 15; A seven-category ordinal scale consisting of: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities. |
| NCT04370834 | Not yet recruiting | Single-centre single arm interventional study | USA | Hospitalized patients with cancer and respiratory complications related to COVID-19 disease(n=200) | Tocilizumab i.v.Patients with stable disease, incomplete benefit, or recurrence of symptoms may receive a second dose | No comparison | Frequency of response; Length of time from level of care to step down level of care Survival at day 60 |
| NCT04363736 | Recruiting  | Multicentre open-Label, Randomized, Study | USA | Hospitalized patients with confirmed severe or moderate COVID-19(n=100) | TCZ 4 mg/kg | TCZ 8 mg/kg | Serum Concentration of interleukin-6 (IL-6), Soluble Interleukin-6 Receptor (sIL-6R), ferritin, C-reactive Protein (CRP), at predefined intervals by Day 28 |
| NCT04372186 | Recruiting  | Multicentre Randomized, Double-Blind, Placebo-Controlled, Study | USA | Hospitalized patients with confirmed COVID-19(n=379) | TCZ 8 mg/kg, with a maximum dose of 800 mg. Up to one additional dose may be given. | IV placebo matched to TCZ. Up to one additional dose may be given. | Cumulative Proportion of Participants Requiring Mechanical Ventilation by Day 28 |
| NCT04377750 | Recruiting  | Multicentre Open Label RCT | Israel | Patients with confirmed COVID-19(n=500) |  Tocilizumab 8 mg/kg (up to total dose of 800 mg) | Placebo: Intravenous administration of 100 ml of normal saline | Survival at day 30. |
| NCT04363853 | Recruiting  | Single-centre single arm, open-label, prospective, blinded, clinical trial | Mexico | Patients with severe or critical COVID-19(n=200) | Tocilizumab | No comparison | At 24h, 48h, 72h, 7days and 14days: Control of hemoglobin, hematocrit, platelets, and leukocytes levels, glucose, uric acid, cholesterol, urea, triglycerides, and creatinine, blood gas At 24hours, 7days and 14days: thorax radiography |
| NCT04377659 | Recruiting  | Single-centre single arm clinical trial | USA | Hospitalized patients with severe COVID-19(n=40) | Participants will receive Tocilizumab 8 mg/kg i.v. at enrollment. Dose will be capped at 800 mg per infusion. If there is no improvement or toxicity, a second dose can be given 24 hrs to 5 days later. | No comparison | Progression of respiratory failure or death at day 14 |
| NCT04331795 | Recruiting  | Single-centre non-randomized clinical trial | USA | Hospitalized patients with confirmed COVID-19(n=50) | Tocilizumab 200mgSecond dose is provisioned if:Increasing supplemental oxygen requirement or Tmax higher than baseline in the 24h following initial tocilizumab administration AND CRP decrease is < 25% at 24 hours following tocilizumab administration and CRP > 40mg/L | Tocilizumab 80mg Second dose is provisioned if:Increasing supplemental oxygen requirement or Tmax higher than baseline in the 24h following initial tocilizumab administration ANDCRP decrease is < 25% at 24 hours following tocilizumab administration and CRP > 40mg/L | Clinical response at 24h; absence of Tmax greater than or equal to 38ºC in the 24-hour period following tocilizumab administration; CRP normalization rate; time to CRP normalization. |
| NCT04359667 | Recruiting  | Single-centre prospective observational Study | Croatia | Patients with severe COVID-19 pneumonia (and/or ARDS)(n=30) | Tocilizumab1 - 8 mg/ kg (maximal 800 mg); can be repeated once more after 12 hours, per clinician`s assessment | No comparison | Serum IL-6 and soluble IL-6 receptor at 24h, 48h, day 7 and day 14 |
| NCT04356937 | Not yet recruiting  | Single-centre prospective placebo-controlled, randomized controlled trial | USA | ICU patients with confirmed COVID-19 and inflammatory markers(n=300) | Tocilizumab 8 mg/kg (maximum 800 mg)  | Placebo | Proportion of patients that require mechanical ventilation at day 28 |
| NCT04394182 | Recruiting | Multicentre prospective single arm study | Spain | Patients with confirmed COVID-19 and inflammatory markers(n=15) | Ultra-Low-dose radiotherapyOxygen Therapy with Nasal Cannula or Ventimask Lopinavir/ritonavir100/400 mg/12h; 7-10 daysHydroxychloroquine200 mg/12hAzithromycin500 mg/24h, 3 daysPiperacillin/tazobactam4 g / 0.5 g administered every 6-8 hours for 5-14 days. Low molecular weight heparinprophylactic dosesUrbason 250mg x 3Tocilizumab600mg single dose | No comparison | Oxygen therapy de-escalation and SapO2 at day 2 |
| NCT04423042 | Not yet recruiting | Single-centre nested cohort study | Canada | Hospitalized patients with suspected or confirmed COVID-19 and hyperinflammation(n=30) | Tocilizumab 8 mg/kg i.v. (up to 800 mg9 with possible repetition within 28 hours but after 12 hours, based on clinical judgment | No intervention | All-cause mortality at day 30 |
| NCT04409262 | Recruiting | Multicentre RCT | USA, Brazil | Hospitalized patients with confirmed COVID-19 (n=450) | Remdesivir loading dose followed by TCZ on day 1, and a once daily remdesivir from day 2 to 10 | Remdesivir loading dose followed by one infusion of placebo on day 1, and a once daily remdesivir from day 2 to 10 | 7-Category Ordinal Scale of Clinical Status on Day 28 |
| NCT04412291 | Not yet recruiting | Single-centre RCT | Sweden | Hospitalized patients with confirmed COVID-19(n=120) | Tocilizumab 8mg/kg single infusion iv (up to 800 mg), second dose if no clinical response after 2 days.Anakinra 400mg per day (divided in 4 doses of 100 mg iv every 6 hours) for 7 days | Standard care | Time to recovery |
| NCT04424056 | Not yet recruiting | Single-centre RCT | France | Hospitalized patients with confirmed COVID-19 (n=216) | Tocilizumab +/- Ruxolitinibor Anakinra +/- Ruxolitinib | Standard care | Ventilation free days at day 28 |
| NCT04412772 | Recruiting | Single-centre RCT | USA | Hospitalized patients with COVID-19 and hyperinflammation status(n=300) | TCZ 8 mg/kg (up to 800 mg). Up to 1 additional dose if clinical worsening | Placebo | Clinical status (on a 7-point ordinal scale) at day 28 |
| NCT04435717 | Recruiting | Single-centre RCT | Spain | Hospitalized patients with mild-moderate COVID-19(n=78) | TCZ 8 mg/kg (up to 800 mg) single dose or TCZ 8 mg/kg in two doses at 0 and 12 hours (up to 800 mg per dose) | Standard care | Change in IL-12 values in from the start of treatment (D0) to days 1 and 3 |
| ChiCTR2000033705 | Recruiting complete | Single-centre nonrandomized observational study | China | Patients with COVID-19 and high levels of IL-6(n=61) | Tocilizumab | Standard care | Clinical status and laboratory examinations |

**Table A.1. Characteristics of the ongoing studies**

Data were retrieved from the Chinese Clinical Trial Registry and Clinicatrial.gov, accessed on 20th June 2020.

§ In the case of multiple active comparator, the table shows Tocilizumab group as intervention and the others as comparisons.

COVID-19: coronavirus disease 2019; BID: twice a day; IMV: invasive mechanical ventilation; RCT: randomized controlled trial

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author** | **Case Control / Cohort**  | **Selection** | **Comparability** | **Outcome/Exposure** | **Score** |
| 1 | 2 | 3 | 4 | 1 2 | 1 | 2 | 3 |
| Alattar et al.1 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Fomina et al. 2 | Cohort | \* |  |  | \* |  |  | \* | \* | 4 |
| Gorgolas et al. 3 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Luo et al. 4 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Morena et al. 5 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Perrone et al. 6 | Cohort | \* |  | \* | \* |  | \* | \* |  | 5 |
| Petrak et al. 7 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Price et al. 8 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Rimland et al. 9 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Sanchez Montalva et al. 10 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Sciascia et al. 11 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Toniati et al. 12 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |
| Xu et al. 13 | Cohort | \* |  | \* | \* |  | \* | \* | \* | 6 |

**Table A.2. Risk of bias of single arm included studies**

The table shows the results of Newcastle-Ottawa-scale (NOS) 14,<sup>14</sup><sup>14</sup><sup>14</sup>[14][13][12][11][10] performed for single-arm included studies. A ‘good’ quality score required three or four stars in selection, one or two stars in comparability, and two or three stars in outcomes. A ‘fair’ quality score required two stars in selection, one or two stars in comparability, and two or three stars in outcomes. A ‘poor’ quality score reflected no or one star(s) in selection, or no stars in comparability, or no or one star(s) in outcomes

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