Supplementary Data

Anti-Rheumatic Drugs as Potential Anti-inflammatory, Immunomodulatory Agents against COVID-19: A Systematic Review

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Table S1. Studies investigating H (CQ) in CoV-2 and some other viruses

Country of Study	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[21]	a prospective open-label randomized controlled (RCT) study	Np=48 /Nc=12	CQ (1g on day 1, then 500 mg/d× 9 days; n=18), HCQ (200 mg BID×10 d; n=12) had beneficial effects on median time in days to clinical recovery (TTCR), duration of admission, and findings on lung CT-Scans in moderate illnesses. CQ had a significantly faster TTCR (5.5 d, P=0.019), and HCQ had a non-significantly faster TTCR (6 d, P=0.049) vs the controls (7.5d). The secondary and safety outcome as median time to viral negative by RT-PCR was shorter in CQ (2.5d, P=0.006) and HCQ (2d, P=0.010) groups vs control (7d). Adverse events were more in the CQ group (44.44%) and HCQ (50%) than controls (16.6%), albeit in mild types.	Fair
China[22]	limited case series as a letter	N=100	Refers to CQ that improved COVID-19 pneumonia, images focus, and reduced the course of illness of more than 100 patients.	Fair
China[23]	RCT	Np=31/Nc=31	Adding HCQ (400 mg/d×5 d) in the treatment of 31/62 patients, reduced the TTCR, radiological results, and improved pneumonia (80.6% vs 54.8%). Adverse events happened more in controls (4 vs 2).	Good
China[24]	RT-RCT	Np=10/Nc=12	In 22 admitted cases: CQ 500 mg/BID for 10d and Lopinavir/Ritonavir, 400/100 mg/BID for 10d as control had similar efficacy in treating COVID-19. Controls became virus-negative faster on day 3, while the CQ group was slightly higher on day 7, day 10, and day 14. Patients treated with CQ appear to recover better and are discharged at a much quicker pace. All adverse events were mild and limited to CQ.	Good
China[25]	retrospective clinical trial study	Np=48/Nc=520	HCQ 200 mg/BID for 7-10 d was significantly associated with lower mortality (P<0.001) and lower hospital stay (<0.05), via attenuation of the inflammatory cytokine storm.	Good
France[26]	Open-label non-randomized clinical trial.	Np=20/Nc=36	HCQ (200 mg. TID× 10 d) reduced the viral load in 20 patients (P<0.001)) and its efficacy was enhanced with azithromycin (100%).	Good
France[27]	Pilot observational cohort	N=80	In an observational cohort of 80 relatively mildly infected inpatients treated with HCQ and azithromycin, except 2 old patients, all cases improved clinically and discharged rapidly. 83% were PCR negative on day 7, and 93% on day 8.	Fair
USA[28]	Retrospective cohort	Np=412 (198 [HCQ]+214 [HCQ+	HCQ without or with azithromycin did not reduce the risk of mechanical ventilation and mortality although an association of increased	Good

		Azithromycin] /Nc=395	overall mortality was seen in those treated with HCQ alone P-0.009).	
USA[29]	multi-center retrospective Cohort	N=2541	In the treatment of 2541 confirmed hospitalized patients with HCQ±, azithromycin reduced mortality. HCQ provided a 66% hazard ratio reduction, and their combination 71% compared to neither treatment (P<0.001).	Good
France[30]	Retrospective Cohort	N=1061	Early administration of HCQ 200mg TDS×10d+azithromycin was safe and associated with a very low fatality (n=8; 0.75%) among the 1061 patients. 2.3% mild adverse events (GI, headache, insomnia, and transient blurred vision) were reported.	Good
USA[31]	retrospective cohort with random sampling	N=1438	Those receiving HCQ (400 mg BID then 200 mg BID) ± azithromycin were more likely than others to be without significant effect on mortality.	Good
USA[32]	Observational cohort	N=1446	Observational study on 1446 consecutive patients showed that HCQ 600 mg BID×1d, then 400 mg/d ×median 5d, in admitted patients was not associated with either greatly lower or increased risk of the composite endpoint of intubation or death.	Good
USA[33]	Observational Retrospective cohort	N=2512/with controls from convenience sample	Preprint: HCQ (800 mg od on day 1 and 400 mg on days 2-5) ±azithromycin was not associated with a survival benefit among hospitalized patients. TCZ demonstrated a trend association towards reduced mortality among 134 ICU recipients.	Good
France[34]	limited case series as a letter	N=11	A prospective study of 11 hospitalized patients using HCQ 600 mg/d for 10d and azithromycin, with 1 death, 2 ICU transfers, 1 Long QT interval, had no sufficient beneficial effect.	Fair
China[35]	open label, RCT	Np=75/Nc=75	75 patients were enrolled in each study arm. Adding HCQ to the standard of care (SOC) did not result in a significantly mild to moderate COVID-19. Adverse events were higher in the HCQ recipients.	Good
France[36]	Cohort study.	N=4642	Revealed no evidence for the efficacy of HCQ (600 mg on day 1, then 400 mg/d for 9d) with or without azithromycin (500 mg on day 1 then 250 mg for 4 d) in 29-days mortality. Significantly, higher rates of discharge were observed by HCQ.	Good
France[37]	observational comparative cohort	N=173	The results do not support HCQ (600 mg/d within 2d of admission) in admitted patients requiring O2 comparing no HCQ.	Fair
USA[38]	Cohort study	N=3372	HCQ + azithromycin did not show beneficial effects on mortality or the need for mechanical ventilation compared to the matched cohort.	Fair
Brazil[39]	Multicenter, RT-RCT	N=630 in 3 groups	Among 504 confirmed COVID-19 patients hospitalized with mild to moderate COVID-19, HCQ 400 mg BID ± azithromycin (P=1.00) did not improve clinical status in 15 d compared to	Good

			SOC. Prolongation of QT and elevation of liver enzymes were more in HCQ groups.	
USA & Canada[40]	RCT	N=491	HCQ 800 mg then 600 mg after 6-8 h, then daily for 4 d did not substantially reduce symptom severity in outpatients with early mild COVID-19 (P=0.21).	Good
USA[41]	Quasi-randomized comparative cohort.	Np=32/Nc=31	In 63 hospitalized COVID-19 patients, HCQ was associated with an increased need for escalation of respiratory support. Also, there were no benefits on mortality and lymphopenia in this cohort.	Good
Brazil[42]	Randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)	N=81	81 patients with SARS-CoV-2 enrolled. High-dose CQ (600 mg. BID for 10 days, or a total dose of 2.7 g) was associated with higher QT prolongation and fatality than low-dose (450 mg. BID stat and then daily for 5 days). Also, there was no difference between treated and non-treated patients in terms of total fatality.	Good
USA[43]	observational retrospective Cohort	Np=21/Nc=13	Preprint: 34 confirmed COVID-19 patients were included in this study. 21 patients received HCQ. HCQ was independently associated with time to negativity test after adjustment for potential confounders in multivariable linear regression analysis.	Good
Spain[44]	observational cohort	N=166	Preprint: in a cohort of 166 patients hospitalized with COVID-19, HCQ with an initial loading dose of 800 mg improved patients' survival when admitted in early stages (P=0.002). There was a non-statistically significant trend towards survival in all groups.	Fair
China[45]	pilot study	N=30	30 patients while one group were given HCQ 400 mg/ day for 5 days and the other group conventional treatment; no significant differences were found in clinical endpoints (viral clearance by day 7 or death).	Fair
USA & Canada[46]	RCT	Np=414/Nc=407	After high-risk or moderate-risk exposure to COVID-19, HCQ did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 d after exposure. Side effects were more in the HCQ group (40.1% vs 16.8%).	Good

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Table S2. Studies investigating CS in CoV-2 and some other viruses.

Country of Study	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[51]	Retrospective observational study (case series)	N=51	The Treatment of 51 COVID-19 patients with the traditional drugs, interferon, lopinavir, ritonavir, and 3-5 days CS (N=10) resulted in the discharge of 50 cases with rapid improvement of clinical and Para clinical parameters (P<0.001). The median hospital stay was 12 d. One patient died.	Fair
China[52]	Observational cohort	N=81	Adding CS (methylprednisolone) for 35 ICU patients resulted in 26 cases discharged from ICU and finally, 16 from the hospital. One died and 2 cases deteriorated	Fair
Canada[53]	limited case series as a letter	N=15	A case series of 15 COVID-19 cases, who received methylprednisolone (60%), or hydrocortisone and dexamethasone revealed a reduction in CRP and O2 and vasopressor need in CRS.	Fair
China[54]	Retrospective cohort	Np=26/Nc=20	26 of 46 patients with severe COVID-19 received methylprednisolone 1-2 mg/kg/day for 5 to 7 days. This was associated with an improvement of the symptoms and chest CT-scan results.	Good
China[55]	Observational study	NP=11/Nc=20	11/31 Covid-19 cases received CS. No association between CS and virus clearance time (HR, 1.26; 95%CI, 0.58-2.74), Hospital stay (HR, 0.77; 95%CI, 0.33-1.78), or duration of symptoms (HR, 0.86; 95%CI, 0.40-1.83) was observed in non-ARDS patients.	Fair
China[56]	Observational study	N=10	Moderate-dose (160 mg/day) methylprednisolone + 20g/day IVIG significantly reduced lung injury and normalized lymphocyte count and CRP levels compared to low dose CS (P<0.05).	Fair
USA[57]	Quasi-experimental prospective cohort	Np=132/Nc=81	An early short course of methylprednisolone 0.5-1 mg/kg/d for 3 d in 132/213 patients with moderate to severe COVID-19 reduced escalation of care, clinical outcomes, and median hospital stay (P<0.001).	Good
Spain[58]	Multicentric, partially randomized, preference, open-label trial	Np=56/Nc=29	Preprint: This open-label trial, of 85 cases, while 56 received 40mg/12h ×3d, then 20mg/12h ×3d methylprednisolone revealed beneficial effects on reducing CRP (0.0003), and outcome, decreasing the risk of composite endpoint of admission to ICU, or death.	Good
UK[59]	RCT	N=6425/Np=2104	Preprint: Dexamethasone 6mg/d reduced 28-d mortality (P<0.001) in those receiving invasive mechanical ventilation, but did not reduce 28-d mortality in those not receiving respiratory support (P=0.14).	Good

China[60]	Case series	N=101/Np=15	This case series of 101 confirmed COVID-19 patients showed that single-pulse methylprednisolone (40-500 mg) had no apparent negative impact on SARS-CoV-2 removal and production of specific IgG while effectively stopping the inflammatory cascade.	Fair
USA[61]	Observational cohort	N=1806/Np=140	CS within 48h of admission was associated with increased risk of mortality or mechanical ventilation in CRP<10 mg/dl (OR, 2.64; 95%CI, 1.39-5.03), and reduced the risk of mortality in CRP>20 mg/dl (odds ratio, 0.23; 95%CI, 0.08-0.70).	Good
China[62]	Multi-centered, retrospective, observational study	Np=43/N=416	In 43/416 COVID-19 patients, CS and concurrent IVIG increased the mortality rate and appear to be useful only in the cases with lower ALCs.	Fair
Japan[63]	case series	Np=7	Methylprednisolone 500 or 1000 mg ×3d, then 1mg/kg×13 d, in 7 mechanically ventilated Japanese patients enabled the doctors to extubate patients within 7d.	Fair
USA[64]	case series	Np=24	3 patients with mild asthma who had received CS before admission represented severe symptoms requiring mechanical ventilation.	Fair
China[65]	Case report	N=2	A couple who were treated with CS and IVIG were successfully discharged in the 2nd week.	Poor
China[66]	Case report	N=1	The treatment of a 45-year-old woman with thalidomide and low-dose methylprednisolone was successful.	Poor
China[67]	Case report	N=1	A 41-year-old man and a 73-year-old man had improvements by CS therapy.	Poor

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Table S3. Studies investigating NSAIDs in CoV-2 and some other viruses.

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
Israel[78]	retrospective cohort	N=403	A retrospective cohort of 403 confirmed COVID-19 cases showed that ibuprofen was not associated with worse clinical outcomes compared to paracetamol or non-pyretic, while 3 patients died in the ibuprofen group.	Fair
Denmark[79]	A nationwide register-based cross-sectional study	N=1872/Np=46	Among the 1872 COVID-19 patients, 46 were exposed to ibuprofen prior to COVID-19 infection. Patients with ibuprofen exposure tended to have hypertension, COPD, and cancer. However, all of the relationships were insignificant (P>0.05).	Fair
South Korea[80]	A nationwide cohort	N=1824	Preprint: NSAID use among 1824 adult patients was associated with worse outcomes among hospitalized users compared to the non-users. This especially increased the risk of primary outcome (OR 1.65, 95%CI 1.21-2.24) and cardiovascular or renal complications (OR 1.87, 95%CI 1.25-2.8).	Fair

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Table S4. Studies investigating Thalidomide in CoV-2 and some other viruses.

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[66]	Case report	N=1	A 45-years-old woman was successfully treated with thalidomide (100mg/day) and low-dose CS.	Poor

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Table S5. Studies investigating IVIG in CoV-2 and some other viruses.

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[99]	Case series	N=3	They reported 3 severe SARS-CoV2 patients who received high-dose IVIG (0.3-0.5 gr/kg/day) with satisfactory recovery.	Poor
China[56]	Observational study	N=10	CS plus 20 g/d IVIG significantly reduced lung injury & normalized lymphocyte count and CRP levels.	Fair
China[97]	Multicenter retrospective cohort study	Np=174/Nc=151	High-dose (>15 g) IVIG, as early administration had beneficial effects on reducing 60-day mortality in critical types. Only in patients with the critical disease, IVIG could significantly reduce the 28-day mortality, decrease the inflammatory response, and improve some organ functions ($p<0.05$).	Good
China[98]	Retrospective study as editorial	N=58	In a retrospective study of 58 severe or critically ill COVID-19 patients, adjunct therapy with IVIG within 48h of hospitalization reduced hospital stay and ventilator use, and improved 28-day mortality.	Fair
China[62]	Multi-centered, retrospective, observational study	Np=43/N=416	In 416 COVID-19 patients, CS and concurrent IVIG increased the mortality rate and appeared to be useful only in the cases with lower ALCs.	Fair
China[65]	Case report	N=2	A couple were treated with CS and IVIG successfully and discharged in 2nd week.	NA

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Table S6. Studies investigating biologics (IL-6 -inhibitors) in CoV-2.

Study Country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[107]	Retrospective observational study	N=21	21 patients with severe or critical criteria of novel-CoV-2 pneumonia enrolled. All patients received TCZ (400 mg. once) +SOC. Within a few days, all symptoms improved and a high percentage of laboratory (e.g. CRP, ALC) and CT-scan findings decreased significantly. Finally, 19 patients were discharged on average 15.1 days after the TCZ.	Fair
Italy[118]	Open-label cohort study	Np=28/Nc=28	A cohort of 28 patients with severe COVID-19 who were treated with sarilumab and 28 contemporary patients received SOC. On day 28, overall clinical improvement and mortality were not significantly different between the two groups. Sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline (P=0.01).	Good
Italy[119]	Retrospective case series	N=15	Sarilumab was administered 400 mg SQ, while 3 received 2 doses. Rapid improvement in respiratory parameters and CRP were observed in 10 (67%). A total of five patients died.	Fair
Italy[120]	Editorial case series	N=8	Adding intravenous sarilumab (400 mg) to SOC, caused at least a 30% reduction in oxygen requirement, and increased oxygenation. The secondary endpoint was the evaluation of CRP, serum amyloid-A, IL-6, D-dimer, LDH, and ALC on days 1, 4, 7. Early treatment led to discharge within 14 days of hospitalization.	Fair
Italy[121]	Case series	N=53	A prospective, case series was done in 53 patients with COVID-19 in both ICU and wards. Sarilumab 400 mg IV was administered on day 1, and patients were followed up for at least 14 days. On day 19, 89.7% of patients significantly improved, 70.6% were discharged, and 85.7% no longer needed oxygen therapy. The overall mortality rate was 5.7%.	Fair
Italy[122]	Pilot prospective open, single-arm, multicenter study (Case series)	N=63	A prospective, case series was done in 63 patients with COVID-19, while 34 patients received TCZ (8 mg/kg) IV, and 29 received TCZ (324 mg) SQ. TCZ decreased fever, PaO2/FiO2, CRP, Ferritin, D-dimer, ALC, and the chance of mortality within 6d of treatment (P<0.05).	Fair
Italy[123]	Prospective cohort study	N=100	In 100 consecutive patients admitted with COVID-19, the response to TCZ 8 mg/kg IV 1-3 doses was rapid, sustained, and associated with significant clinical improvement	Fair

USA[124]	Observational study	N=239 (104 were severe)/Np=153	TCZ-treated cases (n=153) comprised 90% of those with severe disease; 44% of non-severe cases received TCZ for evolving Cytokine storm (CRS). TCZ-treated cases with severe disease had similar survival to the non-severe group (83% vs 91%; P=0.11). After the treatment, oxygenation and inflammatory biomarkers improved higher than expected survival.	Good
USA[125]	Case series	N=27	This small compassionate use study revealed that a single 400 mg IV of TCZ reduced oxygen requirements, inflammation, vasopressor support, and mortality.	Fair
Italy[126]	Case series	N=51	They observed in 51 severe COVID-19 patients, after administration of TCZ a rapid beneficial effect on fever, inflammatory markers happened (P<0.001).	Fair
China[127]	Retrospective cohort study	N=15	15 patients with moderate to severe and critical COVID-19 cases all received at least one dose of TCZ (80 to 600 mg) alone (47%) ± methylprednisolone (53%). After 7 days of treatment, 67% were clinically stable and 20% died. The CRP levels rapidly dropped after the TCZ treatment.	Fair
Spain[128]	Retrospective cohort study	Np=77/Nc=94	Patients in the TCZ group had significantly fewer ICU admission (P=0.005), need for invasive ventilation (P=0.001), and lower mortality rates, especially in the early stages of the inflammatory storm	Good
Italy[129]	Retrospective cohort study	Np=179/Nc=365	Among a cohort of 544 admitted patients, the 179 patients who received TCZ revealed beneficial effects of TCZ (8mg/kg IV and 162 mg SQ) in the reduction of both invasive mechanical ventilation (IMV) and death in patients with severe COVID-19 (AHR O.61, 95%CI 0.4-0.92; P=0.02).	Good
USA[130]	Retrospective cohort study	Np=28/Nc=23	An American cohort of 51 hypoxic COVID-19 patients revealed that TCZ 8 mg/kg was associated with a significantly shorter duration of vasopressor support. Although not significantly, TCZ reduced the time of clinical improvement and the duration of IMV.	Good
Qatar[131]	Retrospective cohort study	N=25	TCZ was associated with a dramatic decline in inflammatory markers, radiological improvements (68% by day 14), and reduced ventilator support (P= 0.001) requirements. 36% discharged from ICU by day 14.	Fair
Turkey[132]	Retrospective cohort study	Np=21/Nc=22	Earlier use of TCZ was beneficial for survival, length of admission, and oxygen support. 3 of 21 cases who received TCZ were transferred to ICU, and none of them died.	Fair
Poland[133]	Retrospective, multi-center study	N=28	TCZ controlled the symptoms of 28 severe COVID-19 patients by reducing inflammatory responses and rapidly improving the clinical status and lung changes	Fair

			in most patients (P<0.001). Only 2 (7%) patients died.	
USA[134]	Retrospective cohort	Np=78/Nc=76	Preprint: TCZ 8 mg/kg (1-2 doses) among 78/154 mechanically ventilated patients with COVID-19 was associated with a decreased likelihood of death despite the higher superinfection occurrence.	Good
Italy[135]	Observational cohort	Np=62/Nc=23	62 patients received TCZ 400-800 mg IV or 324 mg SQ; (based on availability) with a significantly greater survival rate compared to the control patients (HR of death,0.035; 95% ci, 0.004-0.347; P=0.004). The respiratory function improved in 64.8% of the TCZ group while 100% of controls needed MV.	Good
USA[136]	Multicenter, retrospective cohort	N=145	A retrospective study of 145 COVID-19 patients. Near 85% of cases received one dose of TCZ. It was effective in decreasing MV (P=0.002) and mortality (P<0.001), especially when instituted early in the management of critically ill patients	Fair
Spain[137]	Multicenter Cohort Study	Np=261/Nc=969	A total of 1229 and 10673 persons/ days were analyzed. TCZ was associated with a lower risk of death (AHR 0.34, 95%CI 16%-72%, P=0.005) and ICU admission or death (AHR 0.38, 95%CI 19%-81%, P=0.011) among patients with higher CRP levels (>150 mg/dl).	Fair
Italy[138]	Retrospective cohort. Preliminary Results from SMAtteo COvid19 REgistry (SMACORE)	Np=21/Nc=21/ N=112	TCZ did not reduce ICU admission (OR 0.11,95%CI; 0.00-3.38; P=0.22) or mortality rate (OR 0.78,95%CI; 0.06-9.34; P=0.84) among 21 patients compared to SOC.	Good
Italy[139]	retrospective cohort study	Np=32/Nc=33	In a retrospective cohort of 65 patients with severe COVID-19, 32 patients were treated with TCZ. On day 28 the clinical findings and mortality rate were not statistically different between the groups (P=0.15).	Good
Italy, Canada, Denmark, UK, USA, Spain, France, Germany ,Netherland[140]	Double-blind, placebo-controlled trial	Np=294/Nc=144	A new trial as COVACTA, which was conducted by Roche, did not meet its primary endpoint of improved clinical status	Good
Italy[141]	retrospective cohort study	N=457/Np=78	Hyperglycemia had negative impacts on TCZ therapy in both diabetic and non-diabetic patients. TCZ, in hyperglycemic, did not attenuate the risks of the severe outcome as did in normoglycemic cases (p<0.009).	Fair

China[142]	Case report	N=1	A 60-year-old male on maintenance therapy for multiple myeloma was admitted with severe COVID-19. He received TCZ and after 3 days chest tightness improved. Finally, a Chest CT scan cleared after 10d and he was discharged.	Poor
France[143]	Case report	N=1	A 42-year-old male with metastatic sarcomatoid clear cell renal cell carcinoma, after two doses of TCZ alongside antivirals and SOC, experienced clinical improvement.	Poor
China[144]	Case report	N=1	A 57-year-old man, despite multi-drug receiving finally received TCZ and gradually improved and was discharged.	Poor
Italy[145]	Case report	N=1	A 54-year-old obese male with COVID-19 and severe respiratory insufficiency whose condition worsened despite antivirals and non-invasive ventilation was successfully treated with TCZ and NIV.	Poor
Turkey[146]	Case report	N=1	A 41-year-old woman with a history of HTN, presented with COVID-19, and after 3d of deterioration, she was given TCZ 400mg/d and methylprednisolone 60 mg/d, and on day 10 improved dramatically.	Poor
UAS[147]	Case report	N=1	A-56-year-old male with ESRD-secondary to IgA- nephropathy undergoing maintenance hemodialysis for 3 years have reported, who developed COVID-19 pneumonia and gastroenteritis. He was successfully treated with HCQ+TCZ+SOC.	Poor
UAS[148]	Case report	N=1	A-68-year-old man with COVID-19 who was initially treated with HCQ and lenzilumab, deteriorated with respiratory symptoms and an increase in inflammatory markers. He was subsequently treated with TCZ, with significant clinical improvement and a decrease in CRP within 48 h.	Poor
UAS[149]	Cautionary case report.	N=2	Radbel et al. have presented 2 cases of COVID-19 induced CRS with elevated IL-6 and progression to HLH. Both developed poor outcomes despite TCZ treatment.	Poor
Switzerland[150]	Case report	N=1	In a 57-year-old woman with systemic sclerosis who developed COVID-19, the treatment with TCZ led to good control of both scleroderma and arthritis. 4 weeks after the last TCZ infusion, the patients presented with COVID-19. Albeit, this case presented with mild symptoms, that may be due to prophylactic effects of TCZ.	Poor

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Table S7. Studies investigating biologics (IL-1- inhibitors) in CoV-2 (Continued)

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
France[152]	Retrospective cohort Study	Np=52/Nc=44	Both groups received SOC. Anakinra: 100 mg SQ BID×3d, followed by 100 mg/d×7d reduced both the need for invasive MV in ICU and mortality(P<0.0001), without significant side-effects.	Good
Italy[153]	Retrospective cohort study	NP=29/Nc=16	All cases had moderate to severe COVID-19. Only the high dose of anakinra (5 mg/kg. IV twice a day) was effective, with a reduction in CRP, a progressive improvement in respiratory function, and survival (P=0.009).	Good
USA[154]	A small retrospective Case Series	N=14/Np=11	Anakinra could be beneficial in CRS when initiated early after the onset of acute hypoxic respiratory failure	Fair
Greece, Netherland[155]	Case series	Np=8/Nc=29	8 severe COVID-19 cases in Netherland with HLH were given anakinra. This led to less need for vasopressor, significant improvement in respiratory function, and lowered H-Score. Although 3 patients died, it was less than historical controls.	Fair
France[156]	Case series	N=9	A single-center small case series of 9 hospitalized patients, revealed a reduction in O2 need, CRP, and CT-Scan findings	Fair
France[157]	Retrospective cohort	Np=12/Nc=10	They retrospectively compared 22 patients in France with stages 2b and 3 COVID19-pneumonia presenting with acute severe respiratory failure and systemic inflammation who received SOC (n=10), or SOC+ anakinra (n=12). Treatment started with 300mg/d^{-1} for 5d, then tapered in 3d. All the patients in the Anakinra group improved clinically (P<0.01), with no death, significant decreases in O2 need (P<0.05), and more days without IMV (P<0.06), compared to controls.	Fair
Italy[158]	Case report	N=1	A 57-year-old man presented with severe COVID-19. Despite administration of Lopinavir/ ritonavir, HCQ+ azithromycin, the respiratory status deteriorated. Treatment with anakinra 100 mg.q6h.SQ ×7 d was introduced. He improved dramatically and was discharged in good condition.	Poor
Italy[159]	Case report	N=1	A 50-year-old healthy man with COVID-19 who was admitted in ICU received off-label anakinra 200 mg IV followed by 100 mg SQ, QID, due to contraindication of TCZ and remdesivir for hepatic involvement. A sharp reduction of inflammatory markers and liver enzymes happened and respiratory parameters	Poor

			improved by day 13, followed by a favorable radiological evolution	
Turkey[161]	Case report	N=1	Anakinra was useful in a 33-year-old man with COVID-19 and pericarditis.	Poor
Italy[162]	Retrospective cohort study	N=10	A retrospective analysis of 10 patients with COVID-19, and respiratory failure, canakinumab, 300 mg. SQ. was safe and associated with a rapid reduction in the inflammatory response and oxygen requirement	Fair

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 6. Studies investigating biologics (**JAK**- inhibitors) (continued)

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

TableS8. Studies investigating biologics (JAK and TNFα- inhibitors) in CoV-2 (continued)

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[164]	RCT	Np=20/Nc=21	Although no statistical difference was observed, ruxolitinib recipients had a numerically faster clinical improvement. Significant CT improvement (P=0.049) happened on day 14. No death happened in the ruxolitinib group.	Good
Italy[165]	RCT	N=17/Np=7	Ruxolitinib 10 mm BID for 14d, and eculizumab showed significant improvement in respiratory symptoms and radiologic lesions and a decrease in D-dimer levels.	Fair
Italy[166]	Retrospective cohort study	N=191/Np=113	The 2-week case fatality rate was significantly lower in the baricitinib-arm (0 vs 6.4%, P=0.01). ICU admission was 1/113 vs 14/78 (P=0.019) in week-1. The discharge rate was significantly higher in the baricitinib arm at week-1 (P=0.039).	Good
Italy[167]	pilot study	N=12	A pilot study of 12 hospitalized patients with moderate COVID-19 was conducted. Baricitinib tablets added to ritonavir/lopinavir therapy. In the baricitinib-treated group, all clinical characteristics and respiratory functions improved, and CRP levels decreased at week1 and 2 compared to baseline. Discharge in week 2 occurred in 58% of the treated group vs 8% of controls	Fair
Germany[168]	Monocentric, retrospective cohort	N=105/Np=14	14 patients received ruxolitinib due to inflammatory score (CIS) ≥ 10 out of 16 points. A total of 12 achieved a significant reduction of CIS, on day 7 with sustained clinical improvement in 11 cases, without prominent side effects	Fair
China[169]	Multicenter, single-blind, RCT	Np=22/Nc=21	Severe COVID-19 patients receiving ruxolitinib+ SOC (22/43) had a faster clinical improvement and a more favorable safety than controls.	Good
USA[170]	prospective case series	N=86/Np=62	A prospective case series involving patients with immune-mediated inflammatory diseases who were receiving anti-cytokine biologics, other immunomodulatory agents conducted when developed to COVID-19. 86 cases were enrolled, while 62 of them were receiving biologics or JAK-inhibitors. A smaller proportion of hospitalized patients were taking JAK inhibitors or biologics (76%), but not with a significant difference. They conclude that despite the small sample size, the baseline use of biologics and JAK inhibitors are not associated with worse outcomes.	Fair

Study Country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
Italy[171]	Observational, longitudinal trial	Np=20/N=76	Baricitinib 4 mg BID for 2d, then 4mg/d for 7d, demonstrated a marked reduction in serum levels of IL-6, IL-1β, and TNFα, rapid recovery in T& B cell frequencies and an increased Ab-production against SARS-CoV-2 spike protein, reduction in the need to O2.	Good
USA[172]	Multicenter, retrospective cohort	NP=11/N=15	Baricitinib + HCQ was associated with recovery in 11/15 COVID-19 cases. 86.7% of patients had a significant reduction in body temperature and CRP levels, representing 80% survival at the end of the study, with 3 death.	Fair
Italy[174]	Case report	N=1	A 50-year-old man with a previous history of non-Hodgkin lymphoma that was in remission was admitted with COVID-19. After that with severe illness and moderate ARDS baricitinib tablets 4 mg/d was started. Nevertheless, he worsened, with a high IL-6 level of 191 pg/ml. So, CS1mg/kg and TCZ 8mg/kg IV were given, with a drop in IL-6, and he gradually improved in both clinical and CT-scan findings.	Poor
Italy[175]	Case report	N=1	A 71-year-old woman with respiratory failure due to COVID-19, with insufficient response to antiviral, HCQ, and TCZ; treated successfully with baricitinib 4mg/d × 2 week (both respiratory symptoms and CT-Scan findings).	Poor
Italy[176]	Case report	N=1	A favorable course of COVID-19 was observed in an 87-year- old woman despite the underlying RA, while she received baricitinib from 1 year before. This allows speculating that baricitinib had a positive impact on the outcome	Poor
Sout Korea[180]	Case report	N=1	A 53-year-old woman developed COVID-19 during treatment with etanercept and methotrexate for Ankylosing Spondylitis. He had a loss of smell and taste at this time, suggesting that TNFα-inhibitor can delay in dysfunction of smell and taste.	Poor
France[181]	Case report	N=1	The use of Etanercept prior to COVID-19 was not associated with a severe evolution of the COVID-19.	Poor
Germany[182]	cautionary case series	N=7	7 critically ill COVID-19 patients were treated with a single 5 mg/kg infliximab between 0-3 days. A rapid decrease of pro-inflammatory cytokines, and CRP, and LDH was observed, along with clinical improvement in 6 of 7. The 17 cases of the control group showed 35% mortality and prolonged inflammation.	Fair

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