OPEN ACCESS

CLINICAL SCIENCE

Immunomodulatory therapies for SARS-CoV-2 infection: a systematic literature review to inform EULAR points to consider

Alessia Alunno ,[1] Aurélie Najm ,[2] Xavier Mariette,[3] Gabriele De Marco,[4,5] Jenny Emmel,[6] Laura Mason,[6] Dennis G McGonagle,[4,5] Pedro M Machado [7,8,9]

Handling editor Désirée van der Heijde

For numbered affiliations see end of article.

Correspondence to
Dr Alessia Alunno, Rheumatology Unit, Department of Medicine, University of Perugia, 06123 Perugia, Umbria, Italy;
alessia.alunno82@gmail.com

AA and AN contributed equally.

Received 15 December 2020
Revised 24 January 2021
Accepted 27 January 2021
Published Online First 15 February 2021

ABSTRACT

Objective To summarise the available information on efficacy and safety of immunomodulatory agents in SARS-CoV-2 infection.

Methods As part of a European League Against Rheumatism (EULAR) taskforce, a systematic literature search was conducted from January 2019 to 11 December 2020. Two reviewers independently identified eligible studies according to the Population, Intervention, Comparator and Outcome framework and extracted data on efficacy and safety of immunomodulatory agents used therapeutically in SARS-CoV-2 infection at any stage. The risk of bias was assessed with validated tools.

Results Of the 60 372 records, 401 articles were eligible for inclusion. Studies were at variable risk of bias. Randomised controlled trials (RCTs) were available for the following drugs: hydroxychloroquine (n=12), glucocorticoids (n=6), tocilizumab (n=4), convalescent plasma (n=4), interferon beta (n=2), intravenous immunoglobulins (IVIg) (n=2) and n=1 each for anakinra, baricitinib, colchicine, leflunomide, ruxolitinib, interferon kappa and vilobelimab. Glucocorticoids were able to reduce mortality in specific subsets of patients, while conflicting data were available about tocilizumab. Hydroxychloroquine was not beneficial at any disease stage, one RCT with anakinra was negative, one RCT with baricitinib+remdesivir was positive, and individual trials on some other compounds provided interesting, although preliminary, results.

Conclusion Although there is emerging evidence about immunomodulatory therapies for the management of COVID-19, conclusive data are scarce with some conflicting data. Since glucocorticoids seem to improve survival in some subsets of patients, RCTs comparing glucocorticoids alone versus glucocorticoids plus anticytokine/immunomodulatory treatment are warranted. This systematic literature review informed the initiative to formulate EULAR 'points to consider' on COVID-19 pathophysiology and immunomodulatory treatment from the rheumatology perspective.

Key messages

What is already known about this subject?

- The SARS-CoV-2 pandemic is a global health problem. Aberrant host immune response plays an important role throughout the course of mild, moderate and severe COVID-19.
- There is intense investigation to explore the utility of immunomodulatory drugs commonly used in the rheumatology arena as agents that may mitigate against COVID-19 to improve disease prognosis.

What does this study add?

- Robust and reliable evidence of the efficacy of immunomodulatory therapies is scarce, but results from randomised controlled trials (RCTs) ruled out any benefit of hydroxychloroquine at any stage of SARS-CoV-2 infection while demonstrating the ability of some glucocorticoids to reduce mortality in specific patient subsets with severe COVID-19.
- Data from RCTs on tocilizumab are conflicting, and definite conclusions cannot be drawn at this point in time. Anakinra was not effective in the only available RCT, while baricitinib+remdesevir was effective in specific patient subgroups (patients with non-invasive ventilation) in the only available RCT.
- Evidence for several immunomodulatory compounds is scarce, and data from RCTs are required to elucidate their role in the context of different phenotypes of SARS-CoV-2 infection.

How might this impact on clinical practice or future developments?

- This systematic literature review evaluated the evidence pertaining to immunomodulatory drugs where there is some evidence for efficacy in severe COVID-19 and a good safety profile thus far.
- Further evidence is needed regarding the optimal use and consideration of combination therapies for severe disease in a rapidly evolving arena.

INTRODUCTION

SARS-CoV-2 infection encompasses a heterogeneous clinical picture ranging from asymptomatic to multisystem life-threatening manifestations. Although the majority of patients experience only mild to moderate symptoms, a relevant proportion of infected subjects may develop respiratory failure, acute respiratory distress syndrome and death.[1 2] The severest forms of COVID-19 pneumonia are associated with severe pulmonary inflammatory responses, including oedema and inflammatory cell infiltration with severe alveolitis and associated pulmonary immunothrombosis. Beside the

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-219724
► http://dx.doi.org/10.1136/annrheumdis-2021-219957

Check for updates

To cite: Alunno A, Najm A, Mariette X, *et al*. *Ann Rheum Dis* 2021;**80**:803–815.

specific pathogenic effect of SARS-CoV-2, the immune response may be deleterious and excessive since postmortem studies may show excessive immune activation but a paucity of evidence for active viral alveolitis. A vicious circle encompassing the intrapulmonary release of proinflammatory mediators, along with the aberrant activation of immune cells, coagulopathy and histological evidence of haemophagocytosis in patients with more severe COVID-19 demonstrated some features that resembled the macrophage activation syndrome (MAS) also known as secondary haemophagocytic lymphohistocytosis (sHLH).[3 4]

Rheumatologists routinely use immunomodulatory drugs and are well aware of conditions like MAS/sHLH that may be observed as a complication of autoimmune or inflammatory rheumatic and musculoskeletal diseases (RMDs). On this basis, a large number of immunomodulatory drugs used in rheumatology for years have been investigated in SARS-CoV-2 infection, particularly severe COVID-19. This systematic literature review (SLR) was performed to inform the EULAR taskforce responsible for developing the points to consider (PtC) on COVID-19 pathophysiology and immunomodulatory treatment as viewed from the rheumatology perspective. Specifically, the SLR aimed to summarise the available information on the use of immunomodulatory drugs for the management of SARS-CoV-2 infection at any stage.

METHODS

Search methodology

The EULAR task force that developed PtCs on COVID-19 pathophysiology and immunomodulatory treatment from the rheumatology perspective outlined the scope of the systematic literature search, according to the Population, Intervention, Comparator and Outcome approach.[5] Based on a set of research questions encompassing the pathogenesis of SARS-CoV-2 infection, its management with immunomodulatory agents and its possible role as trigger of new-onset RMDs, three separate searches (online supplemental text S1−S4) were performed. The searches were performed in MEDLINE, Embase, The Cochrane Database of Systematic Reviews, CENTRAL and CINAHL. The searches on pathogenesis and RMDs were conducted up to 2 November 2020, while the one on immunomodulatory treatment up to 11 December 2020. The PubMed Similar Articles tool was also used, and a crosscheck of the key scientific journals in general medicine and immunology was performed. Non peer-reviewed literature was excluded given this SLR aimed at informing recommendations. However, given the rapid evolution of knowledge on COVID-19 treatment, a parallel hand search of 'grey literature' consisting only of RCT not yet published in peer-review journals but accessible in press releases or in extenso in preprint repositories was performed. These not yet published RCTs are presented separately and were not used to inform the PtC. In order to ensure this SLR to be as comprehensive as possible and provide an overview of all evidence (regardless of the level), no restriction to specific study design (eg, randomised controlled trials (RCTs)) was defined. The results of the search focused on the pathogenesis of SARS-CoV-2 infection are published elsewhere.

Study selection, data collection and assessment of risk of bias (RoB)

Briefly, original research articles of any study design, published in English, in peer-reviewed journals and addressing adults with proven SARS-CoV-2 infection treated with one or more immunomodulatory agent were eligible (online supplemental text S4). Two reviewers (AA and AN) independently assessed titles and abstracts according to the predetermined eligibility criteria, followed by full-text review. The agreement between reviewers, calculated with the Cohen's kappa, was 0.95. Discrepancies were resolved by discussion. The task force methodologist (PMM) was consulted in the case of uncertainties. Data on patient characteristics, investigated drug administration scheme and comparators and outcomes were extracted. The RoB was assessed using validated tools according to the study design (online supplemental text S5). Only the results pertaining to immunomodulatory therapies are presented here.

RESULTS

Of the 60 372 records yielded by the three searches, 700 were selected for full-text review and seven additional articles were identified by cross-referencing. Of these, 401 articles on 33 therapeutic strategies met the inclusion criteria for the research questions on immunomodulatory treatment of COVID-19 (online supplemental tables S1−S3). Robust evidence was mostly available for moderate to severe/critical COVID-19. The best evidence available for each compound is shown.

Immunomodulatory therapies with evidence on severe (patients on oxygen therapy) or critical (patients in intensive care unit (ICU)) COVID-19

Data from RCTs

A total of 39 RCTs, all at high or unclear RoB, evaluating 13 therapeutic approaches in severe/critical COVID-19 were retrieved by the SLR (online supplemental table S4).

Glucocorticoids

Efficacy

Of the six RCTs on glucocorticoids in severe/critical COVID-19, two investigated dexamethasone (DEX) (one at unclear and one at high RoB), two investigated methylprednisolone (MTP) (one at unclear and one at high RoB) and two investigated hydrocortisone (HCT) (both at unclear RoB). Most of the studies included severe and critical patients with between 15% and 100% of subjects requiring invasive mechanical ventilation (IMV).[6–11] In one study at high RoB, none of the patients needed IMV at enrolment.[11] This, along with the variability of other inclusion criteria, the use of different compounds (eg, long acting vs short acting) and different schedule may have contributed to the conflicting results for the majority of outcomes in the overall analysis (tables 1 and 2). Conversely, subgroup analyses revealed positive results for two (DEX and MTP) out of three compounds with regard to mortality (figure 1). The study from the RECOVERY Collaborative Group (unclear RoB) enrolled 6425 patients with severe COVID-19 of which 2104 were assigned to receive DEX in addition to standard of care (SOC) and 4321 to receive SOC only.[6] The two groups were comparable with regard to need of oxygen therapy/non-invasive or IMV at randomisation. The addition of DEX to SOC reduced mortality but only in patients requiring respiratory support. Likewise, the addition of MTP to SOC in a study at unclear RoB was able to reduce mortality in patients aged 60 years or over.[7] HCT failed to show benefit in reducing mortality in both studies.[9 10] Importantly, the RECOVERY trial also reported that in patients not receiving oxygen therapy, DEX may have a possible (even if not statistically significant) deleterious effect on mortality (OR=1.22, 95% CI 0.93 to 1.61, p=0.14).[6]

Table 1 Effect of immunomodulatory drugs on mortality, assessed by randomised controlled trials, in moderate to severe COVID-19 (with oxygen therapy) and in critical COVID-19 (patients in ICU)

Study, year, ref	Drug, dosage and administration, N	Timepoint (days)†	Mortality intervention (%)	Mortality SOC (%)	Results	Subgroup analysis	% Absolute risk reduction (95% CI)	Risk of bias
Hydroxychloroquine								
Cavalcanti *et al* 2020[16]	HCQ 400 mg twice daily for 7 d. n=221.	Hospital stay	2.3	2.6	No difference between groups.	None performed for mortality.	0.3 (−2.9 to 3.6)	Unclear
Abd-Elsalam *et al* 2020[13]	HCQ 400 mg twice daily on d1 followed by 200 mg twice daily. n=97.	28	6.2	5.2	No difference between groups.	None performed for mortality.	−1.0 (−8.3 to 6.2)	High
RECOVERY 2020[18]	HCQ 800 mg at baseline and at 6 hours, then 400 mg starting at 12 hours after the initial dose and then every 12 hours for the next 9 d or until discharge. n=1561.	28	27.0	25.0	No difference between groups.	No significant RR subgrouping by age, gender, race or ethnic group, days since symptoms, oxygen therapy/IMV and baseline risk.	−1.9 (−4.6 to 0.7)	Unclear
Self *et al* 2020[20]	HCQ 400 mg twice daily for two doses, then 200 mg twice daily for eight doses. n=242.	28	10.3	10.5	No difference between groups.	No significant RR subgrouping by age, gender, race or ethnic group, days since symptoms.	0.2 (−5.3 to 5.8)	Unclear
SOLIDARITY 2020[19]	HCQ 800 mg at baseline and 6 hours, then 400 mg twice daily starting at 12 hours for 10 d.	Hospital stay	11	9.3	No difference between groups.	No significant differences subgrouping by age, gender, days from hospital admission to randomisation, respiratory support, bilateral lung lesions, smoking, various comorbidities, use of corticosteroids and geographic location.	−1.7 (−4.5 to 1.5)	Unclear
Glucocorticoids								
RECOVERY 2020[6]	DEX* 6 mg/d. n=2104.	28	22.9	25.7	Lower in the DEX group.	IMV: RR (95% CI) 0.71 (0.58 to 0.85) NNT 8; Oxygen therapy: RR (95% CI) 0.89 (0.79 to 1.0) NNT 35; no oxygen therapy RR (95% CI) 1.27 (0.99 to 1.61) NNT −27.	2.8 (0.5 to 4.9)	Unclear
Tomazini *et al* 2020[8]	DEX* 20 mg/d intravenous for 5 d and then 10 mg/d intravenous for 5 d. n=151.	28	56.3	61.5	No difference between groups.	None performed for mortality.	5.2 (−5.9 to 16.1)	High
Jeronimo *et al* 2020[7]	MTP* 0.5 mg/kg twice daily intravenous for 5d. n=194.	28	37.1	38.2	No difference between groups.	>60 years of age RR (95% CI) 0.75 (0.55 to 1.0) NNT 7.	1.1 (−8.4 to 10.5)	Unclear
Edalatifard *et al* 2020[11]	MTP* 250 mg/day intravenous pulse for 3 d.	Hospital stay	5.9	42.9	Lower in the MTP group.	NIV: RR (95% CI) 0.13 (0.01–0.90) NNT 2; Reserve mask: RR (95% CI) 0.15 (0.01–1.08) NNT 2; Nasal cannula: RR (95% CI) 0 NNT 5.	37 (15.9 to 55.5)	High
Angus *et al* 2020[9]	HCT* 50 mg intravenous every 6 hours for 7 d.	Hospital stay.	29.9	32.7	No difference between groups.	None performed for mortality.	2.7 (−8.9 to 14.7)	Unclear
Convalescent plasma								
Simonovich *et al* 2020[43]	Convalescent plasma 1 infusion titre >1:800. n=228.	30	11.0	11.4	No difference between groups.	None performed for mortality.	0.46 (−6.2 to 8.7)	Unclear
Li *et al* 2020[41]	Convalescent plasma 1 infusion 4–13 mL/kg of recipient body weight. n=52.	28	15.7	24	No difference between groups.	No significant differences subgrouping by disease severity.	8.3 (−7.4 to 23.7)	High
Agarwal *et al* 2020[42]	Convalescent plasma 2 doses of 200 mL 24 hours apart. n=235.	28	14.5	13.5	No difference between groups.	None performed for mortality.	−0.93 (−7.2 to 6.6)	High
Tocilizumab								

Continued

Table 1 Continued

Study, year, ref	Drug, dosage and administration, N	Timepoint (days)†	Mortality intervention (%)	Mortality SOC (%)	Results	Subgroup analysis	% Absolute risk reduction (95% CI)	Risk of bias
Salvarani *et al* 2020[25]	TCZ 8 mg/kg intravenous within 8 hours from randomisation followed by a second dose after 12 hours. n=60.	30	3.3	1.5	No difference between groups.	None performed for mortality.	−1.8 (−9.9 to 5.5)	Unclear
Hermine *et al* 2020[23]	TCZ, 8 mg/kg, intravenous on day 1 and on day 3 if clinically indicated. n=64.	28	11.1	11.9	No difference between groups.	None performed for mortality.	0.8 (−10.8 to 12.2)	Unclear
Stone *et al* 2020[24]	TCZ 8 mg/kg intravenous single dose. n=161.	28	5.6	3.7	No difference between groups.	No significant differences subgrouping by age, gender, ethrnicity, BMI, diabetes, serum IL-6 and therapy with remdesivir.	−1.93 (−7.2 to 5.1)	Unclear
Salama *et al* 2020[26]	TCZ intravenous 8 mg/kg one or two doses. n=249.	60	11.6	11.8	No difference between groups.	Lower time to death or IMV in Hispanic or Latino treated with TCZ. No significant differences subgrouping by age, region, use of systemic glucocorticoids or antivirals and total number of drug study dose.	0.07 (−6.3 to 7.6)	Unclear
Anakinra								
Mariette *et al* 2020 CORIMUNO-19[30]	ANA 200 mg intravenous twice daily at d 1, 2 and 3, then 100 mg twice daily at d 4 and 100 mg/d at d 5. In case of absence of improvement at d4: 400 mg/d at d 4, 5 and 6, 200 mg/d at d 7 and 100 mg/d at d 8. n=59.	90	27.1	27.3	No difference between groups.	No significant differences subgrouping patients by C reactive protein levels or use of corticosteroids.	0.2 (−15.8 to 16.3)	Unclear
Ruxolitinib								
Cao *et al* 2020[36]	RUXO 5 mg twice daily. n=22.	28	0.0	14.3	No difference between groups.	None performed for mortality.	14.29 (−4.3 to 34.6)	High
Interferon beta								
Davoudi-Monfared *et al* 2020, Rahmani *et al* 2020[33 34]	IFN-beta 250 µg sc eod for 2 weeks. n=46.	28	19	38.5	Lower in the IFN group.	None performed for mortality.	19.4 (−0.4 to 37.5)	High
Monk *et al* 2020[35]	IFN-beta (SNG001) 6 MIU delivered via nebuliser once daily for up to 14 d. n=50.	28	0.0	6.0	No difference between groups.	None performed for mortality.	6 (−2.3 to 16.2)	Unclear
SOLIDARITY 2020[19]	IFN-beta patients receiving high-flow oxygen, ventilation or extracorporeal membrane oxygenation: 10 µg/d intravenous for 6 d. Patients not receiving oxygen therapy or receiving low-flow oxygen therapy: 44 µg at baseline d 3 and d 6.	Hospital stay	12	10.5	No difference between groups.	No significant differences subgrouping by age, gender, days from hospital admission to randomisation, respiratory support, bilateral lung lesions, smoking, various comorbidities, use of corticosteroids and geographic location.	−1.3 (−3.2 to 0.6)	Unclear
IVIg								
Gharebaghi *et al* 2020[39]	IVIg 5 gm 5/day for 3 d. n=30.	Hospital stay.	20.0	48.3	Lower in the IVIg group.	None performed for mortality.	28.3 (4.1 to 48.5)	High
Vilobelimab								
Vlaar *et al* 2020[37]	VILO 800 mg/d intravenous up to seven doses. n=15.	28	13.3	26.7	No difference between groups.	Lower mortality in patients intubated within 6 hours after randomisation and treated with VILO.	13 (−15.8 to 40.4)	Unclear
Baricitinib								

Continued

Table 1 Continued

Study, year, ref	Drug, dosage and administration, N	Timepoint (days)†	Mortality intervention (%)	Mortality SOC (%)	Results	Subgroup analysis	% Absolute risk reduction (95% CI)	Risk of bias
Kalil *et al* 2020[31]	BARI 4 mg/day for 14 days or until hospital discharge +remdesivir 200 mg on d 1 followed by 100 mg/d through 10 d or until hospital discharge or death. n=515.	28	4.7	7.1‡	No difference between groups.	Numerically lower in patients with a baseline ordinal score of 5 or 6.	2.5 (−0.4 to 5.4)	Unclear

The study comparator is standard of care unless otherwise stated.
The absolute risk reduction (ARR) represents the proportion of patients who are spared the adverse outcome (in this case death) as a result of having received the experimental rather than the control therapy. The smaller the treatment effect, the lower the ARR. The number needed to treat, NNT (1/ARR), is the number of patients needed to treat to prevent one additional bad outcome (in this case death). A negative NNT corresponds to a negative ARR, that is, a poorer outcome on the active treatment arm, for example an NNT=−10 indicates that if 10 patients are treated with the new/active treatment, one more would have a bad outcome than if they all received the standard treatment.
*Equivalent doses: DEX=0.75 mg; MTP=4 mg; PDN=5 mg; HCT=20 mg.
†The latest follow-up time available is reported.
‡Comparator in this study is remdesivir 200 mg on day 1 followed by 100 mg/d through 10 d or until hospital discharge or death+placebo+SOC.
ANA, anakinra; BMI, body mass index; d, days ; twice daily, twice daily ; DEX, dexamethasone; eod, every other day; h, hours ; HCQ, hydroxychloroquine; HCT, hydrocortisone; ICU, intensive care unit; IFN, interferon; IL, interleukin; IMV, invasive mechanical ventilation; IVIg, intravenous immunoglobulis; MIU, million international unit; MTP, methylprednisolone; NIV, non-invasive ventilation; RR, relative risk; RUXO, ruxolitinib; SC, subcutaneous; SOC, standard of care; VILO, vilobelimab.

The two studies on DEX yielded conflicting results with regard to the need of IMV; however, a lack of stratification of inpatients with mild to moderate pneumonia receiving oxygen therapy did not allow us to untangle the effect of DEX in patients requiring a low rate of oxygen (1–2 L/min) from the effect in those requiring higher rate (3–15 L/min). In addition, the studies on MTP and HCT assessing the need of IMV[7 10] found no beneficial effect of these compounds. One additional study on HCT in patients with COVID-19 requiring oxygen therapy ≥10 L/min (COVID-19 STEROID) emerged from the search of the 'grey literature', reporting no benefit of HCT on 28-day all-cause mortality.[12]

Safety

Only one study identified safety concerns related to glucocorticoids use in severe COVID-19 with a reported increased insulin use at day 7 in patients treated with MTP+SOC compared with SOC.[7] The other RCTs reported either no difference between groups[8] or descriptive information without statistical assessment of differences (table 3).[9–11]

Hydroxychloroquine

Efficacy

Of the nine RCTs on hydroxychloroquine (HCQ) in severe COVID-19, three studies at high RoB did not report any information regarding the proportions of patients requiring oxygen therapy/NIMV/IMV,[13–15] two studies reported NIMV/IMV as exclusion criterion[16 17] and four studies detailed the proportion of enrolled patients received either oxygen therapy, NIMV or IMV.[18–21] The studies assessing mortality,[13 16 18–20] three at unclear and one at high RoB, agreed that the addition of HCQ to SOC did not provide any beneficial effect. As far as clinical severity is concerned, HCQ did not reduce the need of IMV,[13 16 19] but one RCT at unclear RoB demonstrated a higher risk of progression to IMV in patients treated with HCQ+SOC compared with SOC only[18] (tables 1 and 2). From the parallel hand search in the 'grey literature', we identified one additional RCT on HCQ that was prematurely discontinued due to inefficacy—the ORCHID trial.[22]

Safety

Two studies at unclear RoB alerted on safety issues regarding HCQ. Overall, more adverse events occurred in the HCQ-treated groups. One study reported higher frequency of QTc prolongation and elevation in liver enzyme levels in HCQ-treated patients.[16] The other study reported a greater risk of death in HCQ-treated patients, either from non-SARS-CoV-2 infections or from cardiac causes, although the incidence of arrhythmias was similar across groups.[18] It is important to mention that the schedule of HCQ in the above-mentioned RCTs was higher than that used in rheumatology practice (eg, a stable dose of 800 mg/day or 800 mg/day for a few days followed by 400 mg/day). Furthermore, the combination with other drugs that could prolongate the QT interval such as azithromycin may account for the safety concerns.

Tocilizumab

Efficacy

Three RCTs on tocilizumab (TCZ) at unclear RoB were retrieved.[23–25] In all studies, NIV/IMV represented an exclusion criterion; however, only the CORIMUNO-19 trial excluded also hospitalised patients without need of oxygen therapy, focusing only on patients requiring at least 3 L/min oxygen therapy. In this regard, the observed mortality at

Table 2 Effect of immunomodulatory drugs on invasive and non-invasive ventilation and on oxygen support, assessed by randomised controlled trials, in moderate to severe COVID-19 (with oxygen therapy) and in critical COVID-19 (patients in ICU)

Outcome	Drug	Author, year, ref	Study groups	Results	Risk of bias
Non-invasive or invasive mechanical ventilation	Hydroxychloroquine	Cavalcanti *et al* 2020[16]	SOC+PBO SOC+HCQ + AZT	No difference between groups HCQ OR 1.77 (95% CI 0.81 to 3.87) HCQ+AZT OR 1.15 (95% CI 0.49 to 2.70).	Unclear
		Abd-Elsalam *et al* 2020[13]	SOC SOC+HCQ	No difference between groups (4.1% vs 5.2%, p=0.75).	High
		RECOVERY 2020[18]	SOC SOC+HCQ	Higher progression to IMV in the HCQ group (risk ratio (RR) 1.14; 95% CI 1.03 to 1.27).	Unclear
	Corticosteroids	RECOVERY 2020[6]	SOC+DEX SOC	Risk of progression to IMV was lower in the DEX group than in SOC group (RR 0.77; 95% CI 0.62 to 0.95).	Unclear
		Jeronimo *et al* 2020[7]	SOC+MTP SOC	No difference across groups day 7 hour 2.6 (95% CI 8.6 to 13.6); p=0.654.	Unclear
		Tomazini *et al* 2020[8]	SOC+DEX SOC	6.6 (95% CI 5.0 to 8.2) in the DEX group versus 4.0 ventilator-free days (95% CI 2.9 to 5.4) in the SOC group (difference: 2.26; 95% CI 0.2 4.38; p=0.04).	High
		Dequin *et al* 2020[10]	SOC+HCT SOC+PBO	Of the 16 patients per group without IMV at baseline, 8 (50%) in HCT group and 12 (75%) in the PBO group required subsequent intubation.	Unclear
	Tocilizumab	Hermine *et al* 2020 CORIMUNO-19[23]	SOC+TCZ SOC	At day 14, 12% (95% CI 28% to 4%) fewer patients needed NIV or MV or died in the TCZ group than in the SOC group (24% vs 36%, median posterior HR 0.58; 90% credible interval 0.33 to 1.00).	Unclear
		Stone *et al*[24]	SOC+TCZ SOC+PBO	No difference across groups in the progression to IMV or death. 0.83 (95% CI 0.38 to 1.81; p=0.64).	Unclear
	Anakinra	Mariette *et al* 2020 CORIMUNO-19[30]	SOC+ANA SOC	No difference across groups. The proportion of patients dead or in need of NIV or IMV on day 14. (47%, vs 51%, HR 1.0 (0.6–1.5).	Unclear
	Ruxolitinib (RUXO)	Cao *et al* 2020[36]	SOC+RUXO SOC +100 mg vitamin C	No difference between groups in the need of NIV or IMV and if needed in the duration (p=0.633 and p=0.232).	High
	Interferon (IFN) beta	Davoudi-Monfared *et al* 2020, Rahmani *et al* 2020[33 34]	SOC+IFN beta SOC	No difference between groups in the need of MV and if needed in the duration.	High
		Monk *et al* 2020[35]	SOC+IFN beta PBO +SOC	No significant difference between treatment groups in the odds of intubation or the time to intubation.	Unclear
	IVIg	Tabarsi *et al* 2020[40]	SOC+IVIg SOC	No difference in need for IMV (p=0.39) (n=21 IVIG vs n=10 control group).	High
	Baricitinib	Kalil *et al* 2020[31]	BARI+RDV+ SOC. PBO+RDV+SOC	The incidence of progression to death or NIV or MIV was lower in the RDV+BARI (22.5% vs 28.4%; rate ratio: 0.77; 95% CI 0.60 to 0.98), as was the incidence of progression to death or MIV (12.2% vs 17.2%; rate ratio 0.69; 95% CI 0.50 to 0.95).	Unclear
Oxygen support	Hydroxychloroquine	Cavalcanti *et al* 2020[16]	SOC+PBO SOC+HCQ + AZT	No difference between groups HCQ+AZT OR 1.10 (95% CI 0.60 to 2.03) HCQ OR 1.19 (95% CI 0.65 to 2.21).	Unclear
	Tocilizumab	Stone *et al* 2020[24]	SOC+TCZ SOC+PBO	The median time to discontinuation of supplemental O_2 was 5.0 days (95% CI 3.8 to 7.6) in the TCZ group and 4.9 days (95% CI 3.8 to 7.8) in the placebo group (p=0.69). No difference across groups.	Unclear
	Interferon beta 1a	Davoudi-Monfared *et al* 2020, Rahmani *et al* 2020[33 34]	IFN beta+SOC SOC	No difference between groups.	High

Only studies reporting on the corresponding outcomes are shown.
AZT, azithromycin; BARI, baricitinib; DEX, dexamethasone; HCQ, hydroxychloroquine; HCT, hydrocortisone; ICU, intensive care unit; IFN, interferon; IMV, invasive mechanical ventilation; MTP, methylprednisolone; NIV, non-invasive ventilation; PBO, placebo; RDV, remdesivir; RR, relative risk; RUXO, ruxolitinib; SOC, standard of care; TCZ, tocilizumab.

day 28 in the former two RCTs was rather low (2%–5%), suggesting that they may have enrolled milder patients than CORIMUNO-19. In Stone's study, 16% of patients did not receive oxygen therapy. While Stone *et al*[24] and Salvarani *et al*[25] failed to demonstrate any benefit from the addition of TCZ to SOC for all the outcomes assessed, the CORIMUNO-19 trial demonstrated benefit of adding TCZ to SOC with regard to lower progression to NIV, IMV or death, although day-28 mortality did not differ between groups.

Two additional RCTs on TCZ were identified in the 'grey literature'. The EMPACTA trial, using the same inclusion criteria as CORIMUNO-19, met the composite primary outcome of death or IMV at day 28 and was published in *The New England Journal of Medicine* on 17 December 2020.[26] Conversely, the COVACTA trial did not show a benefit in terms of clinical improvement or mortality in the overall population. Unlike the above-mentioned studies, NIV/IMV were not an exclusion criteria in COVACTA, and of note, 65%–70% of patients were receiving either of the two.[27] However, positive results were reported in a post hoc analysis with a significantly lower proportion of patients experiencing clinical failure in the subgroup not receiving IMV at randomisation (table 4). In patients recently admitted to ICU within 1 day, the REMAP-CAP study was prematurely stopped because of positive results on hospital mortality with TCZ (28% for TCZ vs 35.8% for controls) and on day 90 survival with TCZ: (median HR=1.59 (1.24 to 2.05), probability of superiority of TCZ >99.9%) (table 4).[28] Lastly, an RCT reporting that TCZ was not superior to SOC in improving clinical outcomes at 15 days was published on 22 January 2021.[29]

Safety

The safety profile of TCZ was good, with the study by Stone *et al*[24] showing fewer serious infections in the TCZ group in spite of an increase rate of neutropaenia.

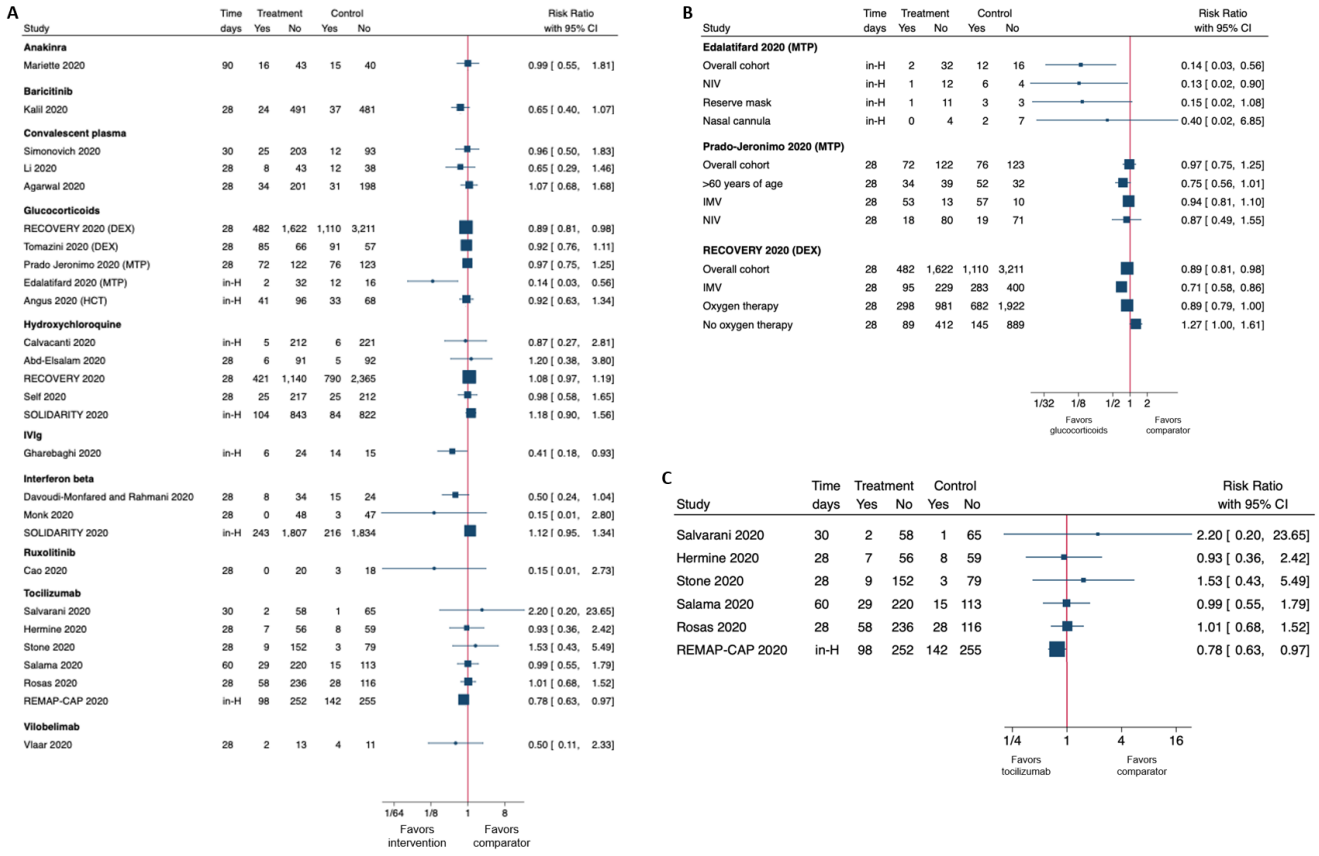

Figure 1 Forest plots showing the risk ratio (RR) and 95% CI for mortality in randomised controlled trials divided by intervention. The latest follow-up available is reported in the timing column. Panel A shows RRs in overall cohorts, panel B shows overall cohorts and subgroup analysis in studies assessing glucocorticoids and panel C shows all studies on tocilizumab (including grey literature).

Anakinra

Efficacy

One RCT assessed anakinra in patients with COVID-19 requiring at least 3 L/min oxygen therapy (CORIMUNO-19) and was published online in *The Lancet Respiratory Medicine* on 22 January 2021.[30] The addition of the drug to SOC failed to improve survival without NIV (including high-flow oxygen) or IMV at day 14 or survival at day 90.

Safety

From a safety perspective, there was a numerical increase of serious infections in the anakinra group.

Baricitinib

Efficacy

At present, the only RCT available on baricitinib in SARS-CoV-2 infection compared remdesevir+baricitinib versus remdesevir+placebo.[31] Patients receiving remdesevir+baricitinib had a median time to recovery of 7 days, as compared with 8 days in the remdesevir+placebo group (rate ratio for recovery: 1.16; 95% CI 1.01 to 1.32; p=0.03), which is statistically significant but clinically probably not meaningful, except in the subgroup of patients with a baseline NIV (including high flow oxygen) in whom median time to recovery was 10 days with the combination therapy, as compared with 18 days in the remdesivir only control group (rate ratio for recovery: 1.51; 95% CI 1.10 to 2.08). It is important to note that the global mortality in the ACTT-2 trial was lower (around 5%) than in other trials like the RECOVERY DEX trial (around 20%) that might explain the modest effect size observed in ACTT-2. Interestingly, the ACTT-4, evaluating the combination of baricitinib and remdesivir compared with DEX and remdesivir is currently ongoing.[32]

Safety

The incidence of adverse events was similar in the two treatment groups.

Other immunomodulatory drugs

Efficacy

The SLR yielded three publications on two RCTs on interferon (IFN) beta,[33–35] one on the Janus kinase inhibitor ruxolitinib,[36] one on anti-C5a vilobelimab,[37] one on colchicine,[38] two on IVIg[39 40] and three on convalescent plasma.[41–43] The studies on vilobelimab and colchicine were at unclear RoB, while all the others were at high RoB. The studies on IFN-beta provided conflicting results on mortality and other clinical outcomes (tables 2 and 3).[33–35] No differences on mortality or in the need of IMV were observed in patients treated with ruxolitinib,[36] while IVIg reduced mortality in hospitalised patients requiring NIMV/IMV.[39] The addition of colchicine to SOC allowed a larger number of patients to achieve cumulative event-free 10-day survival, using a composite outcome including mortality or need of IMV, and a lower number of patients displayed clinical deterioration.[38] However, patients with a slightly milder phenotype not requiring IMV were enrolled. On 24 January 2021 the results of the large COLCORONA trial have been released highlighting that colchicine reduced hospitalisation, use

Table 3 Safety of immunomodulatory drugs assessed by randomised controlled trials in moderate-to-severe COVID-19 (with oxygen therapy) and in critical COVID-19 (patients in ICU)

Drug	Author, year	Study groups	Results	RoB
Hydroxychloroquine	Cavalcanti *et al* 2020[16]	SOC+PBO SOC+HCQ+AZT	Prolongation of the corrected QT interval (p=0.04 for HCQ+AZT; p=0.01 for HCQ) and elevation of liver enzyme p=0.02. More SAE and two deaths in HCQ+AZT groups.	Unclear
	RECOVERY 2020[18]	SOC SOC+HCQ	HCQ group: greater risk of death from cardiac causes (mean (±SE) excess, 0.4±0.2 percentage points) and from non–SARS-CoV-2 infection (mean excess, 0.4±0.2 percentage points).	Unclear
	Tang *et al* 2020[15]	SOC SOC+HCQ	21 (30%) patients HCQ vs 7 (9%) patients PBO.	High
	Huang *et al* 2020[14]	SOC+HCQ SOC	5 patients, 9 AEs in HCQ group, none in control group.	High
	Self *et al* 2020[20]	SOC+HCQ SOC	30 SAEs were reported, including 18 SAEs from 14 patients (5.8%) in the HCQ group and 12 serious adverse events from 11 patients (4.6%) in the control group.	Unclear
	Ulrich *et al* 2020[21]	SOC+HCQ SOC	No difference in AEs between the groups. HCQ was associated with a slight increase in mean corrected QT interval, an increased D-dimer, and a trend towards an increased length of stay.	High
Corticosteroids	Jeronimo *et al* 2020[7]	SOC+MTP SOC+PBO	More insulin at day 7 needed in the MTP group. No more sepsis (but antibiotics in the SOC regimen).	Unclear
	Tomazini *et al* 2020[8]	SOC+DEX SOC	No difference in AEs between groups.	High
	Dequin *et al* 2020[10]	SOC+HCT SOC+PBO	The proportions of bacteraemia were 6.6% in the hydrocortisone group and 11.0% in the placebo group.	Unclear
	Edalatifard *et al* 2020[11]	SOC+MTP SOC	2 patients in each group (5.8% and 7.1%) showed SAE.	High
	Angus *et al* 2020[9]	SOC+HCT SOC	10 patients (2.6%) with SAE, 9 of whom were in the fixed-dose (n=4) and shock-dependent (n=5) HCT groups. Two events (severe neuromyopathy and fungaemia) occurred in the fixed-dose hydrocortisone group.	Unclear
Convalescent plasma	Simonovich *et al* 2020[43]	SOC+convalescent plasma SOC+PBO	No difference in AEs between groups.	Unclear
	Li *et al* 2020[41]	SOC+convalescent plasma SOC	No difference in AEs between groups.	High
	Agarwal *et al* 2020[42]	SOC+convalescent plasma. SOC	No difference in AEs between groups.	High
Tocilizumab	Stone *et al* 2020[24]	SOC+TCZ SOC+PBO	Neutropaenia developed in 22 patients in the TCZ group, as compared with only one patient in the placebo group (p=0.002), but serious infections occurred in fewer patients in the TCZ group (13 (8.1%) vs 14 (17.3%); p=0.03).	Unclear
	Hermine *et al* 2020 CORIMUNO-19[23]	SOC+TCZ SOC	SAE occurred in 20 (32%) patients in the TCZ group and 29 (43%) in the SOC group (p = 0.21). Serious infections occurred in 2 (3%) patients in the TCZ group and 14 (21%) in the control group. Neutropaenia developed in 4 (6%) in the TCZ group and 0 in the control group.	Unclear
Colchicine	Deftereos *et al* 2020[38]	SOC+COL SOC	Diarrhoea was more frequent in the colchicine group (25 patients(45.5%) versus nine patients (18.0%); p = 0.003).	Unclear
Ruxolitinib	Cao *et al* 2020[36]	SOC+RUXO SOC	No differences between groups 15 patients (71.4%) PBO group and 16 (80%) in RUXO group.	High
Interferon beta	Davoudi-Monfared *et al* 2020, Rahmani *et al* 2020[33 34]	SOC+IFN beta SOC	No differences between groups (all p>0.05). A total of 47 common AEs in the IFN and 62 in the control group.	High
	Monk *et al* 2020[35]	SOC+IFN beta PBO+SOC	Treatment emergent AEs were more common in the IFN group.	Unclear
Vilobelimab	Vlaar *et al*[37]	SOC+VIL SOC	Numbers of SAE were similar between groups (60% of patients in the IFX-1 group vs 47% in the control group).	Unclear
Baricitinib	Kalil *et al* 2020[31]	BARI+RDV+ SOC PBO+RDV+SOC	No difference in AEs between groups.	Unclear

Only studies reporting on safety are shown.
AE, adverse event; AZT, azithromycin; COL, colchicine; DEX, dexamethasone; HCQ, hydroxychloroquine; HCT, hydrocortisone; IFN, interferon; MTP, methylprednisolone; MV, mechanical ventilation; PBO, placebo; RR, relative risk; RUXO, ruxolitinib; SAE, severe adverse event; SE, standard error; SOC, standard of care; TCZ, tocilizumab; VIL, vilobelimab.

of ventilation and mortality.[44] Vilobelimab was not effective on any of the outcomes assessed (table 4). All studies on convalescent plasma failed to show any efficacy on 28-day mortality, progression to severe disease[42] or clinical improvement at 28[41] or 30[43] days. On the day of submission of this article, a press release announced that the phase III RUXCOVID study evaluating ruxolitinib+SOC compared with placebo+SOC in patients with COVID-19 did not meet its primary endpoint of reducing the number of hospitalised patients with COVID-19 who experienced severe complications (death, mechanical ventilation or ICU care).[45] Finally, a press release on 2 July 2020 reported the failure of a phase III trial assessing sarilumab in critical patients (requiring IMV) with COVID-19,[46] while in the above-mentioned REMAP-CAP study (grey literature) assessing TCZ and sarilumab demonstrated efficacy of the latter in improving survival and other outcomes.[28]

Safety

Ruxolitininb and vilobelimab and convalescent plasma showed a good safety profile. Conversely, data were conflicting for IFN-beta, not reported for IVIg and worse safety profile for colchicine since authors highlighted a higher frequency of diarrhoea in colchicine-treated patients.

Data from prospective or retrospective controlled studies

Prospective controlled studies were identified as best available evidence for eight therapeutic strategies, three of which

Table 4 'Grey literature' concerning randomised controlled trials

Drug	Study name	Author, year	Study groups	Efficacy	Safety	Risk of bias
Tocilizumab	REMAP-CAP	Gordon *et al* 2020	SOC* SOC* +TCZ SOC* +SARI	Compared with control, median adjusted ORs for hospital survival were 1.64 (95% CrI 1.14, 2.35) for TCZ and 2.01 (95% CrI 1.18 to 4.71) for SARI. TCZ and SARI were effective across all secondary outcomes, including 90-day survival, time to ICU and hospital discharge and improvement in the WHO ordinal scale at day 14.	Nine serious adverse events reported in the TCZ group including one secondary bacterial infection, five bleeds, two cardiac events and one deterioration in vision. Eleven serious adverse events in the control group, four bleeds and seven thromboses. No serious adverse events in the SARI group.	Unclear
TCZ	COVACTA	Rosas *et al* 2020	SOC† +PBO SOC† +TCZ	No difference between groups in mortality at day 28 between TCZ (19.7%) and PBO (19.4%) (difference, 0.3% (95% CI −7.6 to 8.2); nominal p=0.94). Post hoc analysis on patients not on IMV: Among patients not receiving MV at randomisation, less patients in the TCZ group experienced any clinical failure at day 28 compared with PBO (29% vs 42.2%) HR 0.614; 95% CI 0.40 to 0.94; nominal p=0.03).	Serious adverse events occurred in 34.9% of 295 patients in the TCZ arm and 38.5% of 143 in the PBO arm.	Unclear

*Standard care of each recruiting site. Since participants could be randomised to other interventions within other domains, depending on domains active at the site, patient eligibility and consent (see www.remapcap.org). Randomisation to the corticosteroid domain for COVID-19 closed on 17 June 2020.[12] Thereafter, corticosteroids were allowed as per recommended standard of care.
†Standard care per local practice (antiviral treatment, low-dose steroids, convalescent plasma and supportive care) was permitted; however, concomitant treatment with another investigational agent (except antivirals) or any immunomodulatory agent was prohibited.
AE, adverse event; AZT, azithromycin; COL, colchicine; CrI, credibility interval; DEX, dexamethasone; HCQ, hydroxychloroquine; HCT, hydrocortisone; ICU, intensive care unit; MTP, methylprednisolone; PBO, placebo; RUXO, ruxolitinib; SAE, severe adverse event; SARI, sarilumab; SE, standard error; SOC, standard of care; TCZ, tocilizumab.

using a combination of two immunomodulatory drugs (online supplemental table 5).

Glucocorticoids+TCZ

Efficacy

Three studies assessed this therapeutic strategy.[47–49] Ramiro *et al*[47] enrolled patients requiring any kind of oxygen support, reporting that the proportion of patients receiving IMV was higher in the cohort of patients treated with SOC versus those receiving TCZ (15% vs 1%). The treatment protocol included sequential MTP and TCZ, the latter added if lack or clinical response to MTP within 2–5 days. Historical control groups were identified among patients referred to the same centre in the previous month and receiving SOC only. Significant positive effects were observed in the TCZ+MTP group with regard to mortality, IMV, oxygen support, clinical improvement and time to discharge. Of note, day-28 mortality rate in the control group was high (48%).

Likewise, Sanz Herrero *et al*[49] compared patients receiving TCZ either monotherapy or in combination with MTP and reported that combination therapy was superior to monotherapy in reducing the risk of death. On the contrary, Gupta *et al*[50] reported that the association between TCZ treatment and mortality was similar in patients having received or not glucocorticoids on ICU admission (HRs (95% CI) 0.68 (0.46 to 0.99) and 0.71 (0.53 to 0.96)), respectively.

Safety

One study at unclear RoB reported that although the overall rate of adverse events was comparable in the treatment groups, there was a trend towards more pulmonary embolism in the TCZ+glucocorticoids group (p=0.059). Arrhythmias occurred less frequently, although not significantly, in the TCZ+glucocorticoids group (p=0.265).[47]

Glucocorticoids+baricitinib

Efficacy

The combination of baricitinib and glucocorticoids added to SOC was assessed in a study at high RoB.[51] Patients with severe COVID-19, half of which were receiving NIV (IMV was an exclusion criterion) received three consecutive days of pulse MTP therapy (80, 125 or 250 mg/day) followed by prednisone at a starting dose of 30 mg/day tapered until discontinuation within 7–10 days. Those receiving only MTP were compared with those receiving also baricitinib from day 3 (2 or 4 mg/day), and the combination therapy (regardless of the baricitinib dose) was linked to more pronounced clinical improvement, a lower use of supplemental oxygen both at discharge and 1 month later was compared with MTP+SOC.

Safety

A number of adverse events occurred in the two treatment groups, including infectious and cardiac adverse events, but the authors did not flag any specific scenario attributable to baricitinib. Of particular interest, occurrence of venous thromboembolism, a class warning for JAK inhibitors, was similar in the two treatment groups.

Other immunomodulatory drugs

A few small prospective studies at variable RoB evaluated mavrilimumab,[52] lenzilumab,[53] eculizumab,[54] sarilumab,[55] recombinant human IL-7[56] and the combination of ruxolitinib+eculizumab,[57] ruxolitinib+glucocorticoids[58] and cyclosporin+glucocorticoids.[59] However, none of them provided solid positive results.

One retrospective controlled study of infliximab at high RoB showed comparable mortality rate and need of IMV in 17 patients with COVID-19 treated with SOC versus seven patients receiving infliximab in addition to SOC. In the 'grey literature', we came across other ongoing studies with infliximab (ACTIV-1: NCT04593940 and CATALYST: ISRCTN40580903) and adalimumab (AVID-CC: ISRCTN33260034).[60] One retrospective study explored anakinra in combination with glucocorticoids reporting a possible benefit in reducing mortality.[61]

Data from non-controlled studies

Canakinumab was evaluated in one retrospective non-controlled study and one case report,[62 63] tesidolumab was assessed in one retrospective study[64] and itolizumab was assessed in a prospective non-controlled study.[65] These studies showed favourable, although very preliminary results, that required to be confirmed in controlled studies.

Table 5 Effect and safety of immunomodulatory drugs assessed in mild COVID-19 (without oxygen support)

Outcome	Drug	Author, year (ref)	Study design	Study groups	Results	Risk of bias
Mortality	Hydroxychloroquine	Lyngbakken *et al* 2020[78]	RCT	SOC+HCQ SOC	No difference between groups.	High
		Ulrich *et al* 2020[21]	RCT	SOC+HCQ SOC	No difference between groups at day 14 for the composite criteria (death, ICU admission, mechanical ventilation, extracorporeal membrane oxygenation and/or vasopressor use).	High
	Baricitinib	Bronte *et al* 2020[74]	Prospective	SOC+BARI SOC	1/20 (5%) in BARI group versus 25/56 (45%) SOC group (p<0.001).	High
	IFN alpha	Wang *et al* 2020[71]	Prospective	SOC+IFN alpha-2b SOC	None of the patients died in any group.	High
Discharge/Time to Hospital Discharge	Hydroxychloroquine	Lyngbakken *et al* 2020[78]	RCT	SOC+HCQ SOC	No difference between groups p by log-rank test=0.71.	High
	Baricitinib	Cantini *et al* 2020[73]	Prospective	SOC+BARI SOC	Discharge at week 2 occurred in 58% (7/12) of the BARI-treated patients versus 8% (1/12) of controls (p=0.027).	High
	Leflunomide	Wang *et al* 2020[69]	RCT	SOC+LEF SOC	No difference between groups 29.0 (IQR 19.3–47.3) days versu 33.0 (IQR 29.3–42.8) days p=0.170.	High
	IFN alpha	Wang *et al* 2020[71]	Prospective	SOC+IFN alpha-2b SOC	Shorter time to discharge in the treatment group. Even shorter if early intervention.	High
Negative conversion of SARS-CoV-2	Hydroxychloroquine	Mitja *et al* 2020[66]	RCT	SOC+HCQ SOC	No difference across groups day 3 and day 7.	Unclear
		Chen *et al* 2020[17]	RCT	SOC+HCQ SOC	No difference in time to negative PCR at day 14: 5 days (95% CI 1 to 9 days) and 10 days (95% CI 2 to 12 days) for the HCQ and SOC groups, respectively (p=0.40).	High
		Omrani *et al* 2020[68]	RCT	SOC+HCQ SOC	No difference across groups day 6 negative PCR (p=0.821) HCQ+AZT 16/152 (10.5%), HC 19/149 (12.8%), placebo 18/147 (12.2%). Day 14 (p=0.072) HC +AZ 30/149 (20.1%), HC 42/146 (28.8%), placebo 45/143 (31.5%).	High
	Leflunomide	Hu *et al* 2020[70]	RCT	SOC+LEF SOC	5 days LEF versus 11 days control group (p=0.046).	High
		Wang *et al* 2020[69]	RCT	SOC+LEF SOC	No difference between groups HR for negative RT-PCR, 0.70; (95% CI 0.391 to 1.256; p=0.186).	High
	IFN alpha	Wang *et al* 2020[71]	Prospective	SOC+IFN alpha-2b SOC	Faster in the treatment group.	High
	IFN kappa	Fu *et al* 2020[72]	RCT	SOC+IFN kappa SOC	Significantly shorter time to viral RNA negative conversion in IFN group.	Unclear
Treatment emergent AEs	Hydroxychloroquine	Mitjà *et al* 2020[66]	RCT	SOC+HCQ SOC	AE in SOC 16/184 (8.7%)<121/169 (72.0%) in HCQ group.	Unclear
		Skipper *et al* 2020[67]	RCT	SOC+HCQ SOC	AEs with HCQ >PBO at day 5 (43% (92 of 212) versus 22% (46 of 211); p<0.001). GI symptoms in 31% (66 of 212).	Unclear
		Chen *et al* 2020[17]	RCT	SOC+HCQ SOC	No SAE reported. Grades 1 and 2 HCQ-related adverse events included headache (21.1%), dizziness (5.3%), gastritis (5.3%), diarrhoea (5.3%), nausea (5.3%) and photophobia (5.3%).	High
		Omrani *et al* 2020[68]	RCT	SOC+HCQ SOC	No SAE. No association (p=0.708) between study group and development of pneumonia, which was diagnosed in seven participants (1.5%): three (2.0%) in the HC+AZ group, one (0.7%) in the HC group and three (2.0%) in the placebo group.	High
		Ulrich *et al* 2020[21]	RCT	SOC+HCQ SOC	No difference in AEs between the groups. HCQ was associated with a slight increase in mean corrected QT interval, an increased D-dimer and a trend towards an increased length of stay.	High
	Leflunomide	Hu *et al* 2020[70]	RCT	SOC+LEF SOC	ALT and AST reversibly increased LEF group (p=0.049 and p=0.176, respectively).	High
		Wang *et al* 2020[69]	RCT	SOC+LEF SOC	No difference in AEs between the groups.	High
	Tocilizumab	Zhao *et al* 2020[75]	RCT	SOC+favipiravir SOC+favipiravir +TCZ	Nine adverse reactions were reported in the combined treatment group, and two adverse reactions were reported in the favipiravir group and the TCZ group, respectively.	High
	Baricitinib	Cantini *et al* 2020[73]	Prospective	SOC+BARI SOC	No SAEs. 1 patient with transaminases elevation in the BARI group.	High
		Bronte *et al* 2020[74]	Prospective	SOC+BARI SOC	No SAEs.	High
	IFN alpha	Wang *et al* 2020[71]	Prospective	SOC+IFN alpha-2b SOC	No difference in AEs between the groups.	High
	IFN kappa	Fu *et al* 2020[72]	RCT	SOC+IFN kappa SOC	No SAEs.	Unclear

Only studies reporting on the corresponding outcome are shown.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZT, azithromycin; BARI, baricitinib; COL, colchicine; DEX, dexamethasone; GI, gastrointestinal; HCQ, hydroxychloroquine; HCT, hydrocortisone; IFN, interferon; LEF, leflunomide; MTP, methylprednisolone; PBO, placebo; RT-PCR, real time PCR; RUXO, ruxolitinib; SAE, severe adverse event; SAEs, serious adverse events; SE, standard error; SOC, standard of care; TCZ, tocilizumab.

Immunomodulatory therapies with evidence on mild COVID-19 (without oxygen therapy)

Six immunomodulatory strategies were assessed in RCTs at high or unclear RoB enrolling patients with mild to moderate COVID-19 (table 5).

Hydroxychloroquine

Efficacy

Five RCTs evaluated HCQ in mild to moderate COVID-19,[17 21 66–68] but none of them demonstrated any benefit with the addition of this drug to SOC (including in milder non-hospitalised patients.[66 67]

Safety

In line with what was reported from studies in severe COVID-19, the RCTs enrolling mild to moderate COVID-19 highlighted safety concerns for HCQ since a higher number of adverse events were observed in the HCQ-SOC group compared with SOC.

Other immunomodulatory drugs

Two small RCTs at high RoB reported on leflunomide.[69 70] One study observed no difference in length of hospital stay,[69] while conflicting results were reported by both studies with regard to a possible effect on negative conversion of SARS-CoV-2. Safety concerns were raised by one of the studies with increased liver enzymes in leflunomide-treated patients.[70]

IFN-alpha[71] and IFN-kappa[72] reduced the time to negative conversion of SARS-CoV-2 in two studies. Two prospective studies on baricitinib at high RoB provided conflicting results for every assessed outcome and only agreed on the fact that addition of baricitinib to SOC did not worsen the safety profile of the therapeutic strategy.[73 74] One small study evaluated TCZ+-favipavir demonstrating positive effects on lung inflammation.[75]

DISCUSSION

Our SLR has shown that despite the large bulk of articles investigating several immunomodulatory drugs for the treatment of SARS-CoV-2 infection, most studies are at high or unclear RoB, and robust evidence on efficacy is available only for a few drugs and for a low number of outcomes. In particular, data from RCTs showed that the addition of HCQ to SOC was not beneficial at any stage of SARS-CoV-2 infection, while glucocorticoids may reduce mortality in some subgroups of patients with moderate, severe or critical COVID-19. The latter evidence is mainly driven by the large RECOVERY trial.[6] Regarding TCZ, three available RCT were positive, but three other RCTs are negative. Thus, TCZ could have a place in some specific subgroups that remain to be determined.[23 76]

The SLR identified a number of pitfalls that prevented the comparison of retrieved studies and constrains results interpretation. First, heterogeneity of inclusion criteria even in studies claiming to assess the same patient subgroup (eg, severe COVID-19) was often observed. In fact, various parameters, such as the partial pressure of oxygen (PaO_2)/fractional inspired oxygen ratio, C reactive protein level and peripheral oxygen saturation to cite a few, with different cut-off values, have been used to classify patients contributing to a relevant selection bias. We tried to overcome this issue and harmonise the presentation of results using a framework inspired by one the WHO scales.[77]

In RCTs, the definition of 'standard of care' was also highly variable making data interpretation difficult. Every immunomodulatory drug that has been assessed was added on top of SOC and compared (with a few exceptions) with SOC alone. However, in COVID-19, SOC changed rapidly, and the approaches recommended as SOC in March 2020 were not the same as in the subsequent months. Moreover, other factors such as local/national regulations or recommendations, criteria for hospital admission/IMV or differing drug availability increased study variability even if published within the same timeframe. In addition, in some studies, the treatment, including glucocorticoids, interferon or other immunomodulatory drugs, was left at the discretion of the treating physician, meaning that a subgroup of the intervention group could receive other drugs in a non-standardised manner, subsequently affecting the interpretability of the results.

In prospective observational studies, the main pitfall was that the control groups were often historical and thus not comparable with the studied group, even if adjusted for baseline characteristics, given the rapid evolution in the treatment of the disease. Finally, yet importantly, study outcomes along with the timing of their assessment largely varied across studies.

In conclusion, this SLR informed the EULAR initiative to formulate PtC on COVID-19 pathophysiology and immunomodulatory therapies. However, the results of the present SLR also underscored the need of RCTs with standardised inclusion criteria and outcomes in order to robustly elucidate the effect of immunomodulatory drugs at different stages of SARS-CoV-2 infection and ultimately improve the care and prognosis of affected people. Another important aspect to be further explored is the identification of factors predicting efficacy of the selected drug(s) in a specific population.

Author affiliations
[1]Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy
[2]Institute of Infection, Immunity and Inflammation, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
[3]Department of Rheumatology, Université Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, INSERM UMR1184, Le Kremlin Bicêtre, France
[4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[5]The NIHR Leeds Biomedical Research Centre, Chapel Allerton Hospital, Leeds, UK
[6]Library & Evidence Research Centre, Medical Education, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[7]Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK
[8]Centre for Rheumatology & Department of Neuromuscular Diseases, University College London, London, UK
[9]National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC), University College London Hospitals (UCLH) NHS Foundation Trust, London, UK

Twitter Pedro M Machado @pedrommcmachado

Contributors All authors contributed and finally approved the current manuscript.

Funding This work was funded by European League Against Rheumatism (CLI122). PMM is supported by the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre.

Disclaimer The views expressed are those of the authors and not necessarily those of the (UK) National Health Service, NIHR or the Department of Health.

Competing interests XM has received consulting and/or speaker's fees from BMS, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer, Servier and UCB, all unrelated to this manuscript. DGM has received consulting and/or speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche and UCB, all unrelated to this manuscript. PMM has received consulting and/or speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche and UCB, all unrelated to this manuscript.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Alessia Alunno http://orcid.org/0000-0003-1105-5640
Aurélie Najm http://orcid.org/0000-0002-6008-503X
Pedro M Machado http://orcid.org/0000-0002-8411-7972

REFERENCES

1 Wiersinga WJ, Rhodes A, Cheng AC, *et al*. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;324:782.
2 Wong CKH, Wong JYH, Tang EHM, *et al*. Clinical presentations, laboratory and radiological findings, and treatments for 11,028 COVID-19 patients: a systematic review and meta-analysis. *Sci Rep* 2020;10:19765.
3 McGonagle D, Sharif K, O'Regan A, O'Regan A, *et al*. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020;19:102537.
4 Alunno A, Carubbi F, Rodríguez-Carrio J. Storm, Typhoon, cyclone or Hurricane in patients with COVID-19? beware of the same storm that has a different origin. *RMD Open* 2020;6:e001295.
5 Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions, version 5.1.0*, 2013.
6 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med Overseas Ed* 2020:NEJMoa2021436.
7 Jeronimo CMP, Farias MEL, Val FFA, *et al*. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa1177. [Epub ahead of print: 12 Aug 2020].
8 Tomazini BM, Maia IS, Cavalcanti AB, *et al*. Effect of dexamethasone on days alive and Ventilator-Free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the Codex randomized clinical trial. *JAMA* 2020;324:1307.
9 Angus DC, Derde L, Al-Beidh F, *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:E1–13.
10 Dequin P-F, Heming N, Meziani F, *et al*. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:1298.
11 Edalatifard M, Akhtari M, Salehi M, *et al*. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020;56. doi:10.1183/13993003.02808-2020. [Epub ahead of print: 24 Dec 2020].
12 WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, *et al*. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;324:E1–12.
13 Abd-Elsalam S, Esmail ES, Khalaf M, *et al*. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. *Am J Trop Med Hyg* 2020;103:1635–9.
14 Huang HD, Jneid H, Aziz M, *et al*. Safety and effectiveness of hydroxychloroquine and azithromycin combination therapy for treatment of hospitalized patients with COVID-19: a Propensity-Matched study. *Cardiol Ther* 2020;9:523–34.
15 Tang W, Cao Z, Han M, *et al*. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849.
16 Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med* 2020;383:e119.
17 Chen C-P, Lin Y-C, Chen T-C, *et al*. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). *PLoS One* 2020;15:e0242763.
18 RECOVERY Collaborative Group, Horby P, Mafham M, *et al*. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;383:2030–40.
19 WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 — interim who solidarity trial results. *N Engl J Med Overseas Ed* 2020:NEJMoa2023184.
20 Self WH, Semler MW, Leither LM, *et al*. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:2165.
21 Ulrich RJ, Troxel AB, Carmody E, *et al*. Treating COVID-19 with hydroxychloroquine (teach): a multicenter, double-blind randomized controlled trial in hospitalized patients. *Open Forum Infect Dis* 2020;7:ofaa446.
22 Hernandez AV, Roman YM, Pasupuleti V, *et al*. Update alert 3: hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19. *Ann Intern Med* 2020;173:W156–7.
23 Hermine O, Mariette X, Tharaux P-L, *et al*. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;181:32.
24 Stone JH, Frigault MJ, Serling-Boyd NJ, *et al*. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* 2020;383:2333–44.
25 Salvarani C, Dolci G, Massari M, *et al*. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;181:24–31.
26 Salama C, Han J, Yau L, *et al*. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* 2021;384:20–30.
27 Furlow B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. *Lancet Rheumatol* 2020;2:e592.
28 The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19 – preliminary report. *medRxiv* 2020.
29 Veiga VC, Prats J, Farias DLC. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2020.
30 Mariette X, Hermine O, Tharaux P-L. Effect of Anakinra vs usual care in adults hospitalized with COVID-19 and mild-to-moderate pneumonia: a randomized clinical trial. *Lancet Respir Med* 2020.
31 Kalil AC, Patterson TF, Mehta AK, *et al*. Baricitinib plus Remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2020. doi:10.1056/NEJMoa2031994. [Epub ahead of print: 11 Dec 2020].
32 NIH. Adaptive COVID-19 treatment trial 4 (ACTT-4). Available: https://clinicaltrials.gov/ct2/show/NCT04640168
33 Davoudi-Monfared E, Rahmani H, Khalili H. Efficacy and safety of interferon beta-1a in treatment of severe COVID-19: a randomized clinical trial. *Antimicrob Agents Chemother* 2020.
34 Rahmani H, Davoudi-Monfared E, Nourian A, *et al*. Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. *Int Immunopharmacol* 2020;88:106903.
35 Monk PD, Marsden RJ, Tear VJ, *et al*. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020. doi:10.1016/S2213-2600(20)30511-7. [Epub ahead of print: 12 Nov 2020].
36 Cao Y, Wei J, Zou L, *et al*. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020;146:137–46.
37 Vlaar APJ, de Bruin S, Busch M, *et al*. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. *Lancet Rheumatol* 2020;2:e764–73.
38 Deftereos SG, Giannopoulos G, Vrachatis DA, *et al*. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019. *JAMA Netw Open* 2020;3:e2013136.
39 Gharebaghi N, Nejadrahim R, Mousavi SJ, *et al*. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. *BMC Infect Dis* 2020;20:786.
40 Tabarsi P, Barati S, Jamaati H, *et al*. Evaluating the effects of intravenous immunoglobulin (IVIg) on the management of severe COVID-19 cases: a randomized controlled trial. *Int Immunopharmacol* 2021;90:107205.
41 Li L, Zhang W, Hu Y, *et al*. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* 2020;324:460.
42 Agarwal A, Mukherjee A, Kumar G. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial). *BMJ*;151:m3939.
43 Simonovich VA, Burgos Pratx LD, Scibona P, *et al*. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med* 2020. doi:10.1056/NEJMoa2031304. [Epub ahead of print: 24 Nov 2020].
44 The Canadian. 'Major breakthrough' | Large study shows effectiveness of colchicine to treat COVID-19. Available: https://thecanadian.news/2021/01/23/major-breakthrough-large-study-shows-effectiveness-of-colchicine-to-treat-covid-19/
45 Novartis. Novartis provides update on RUXCOVID study of ruxolitinib for hospitalized patients with COVID-19, 2020. Available: https://www.novartis.com/news/media-releases/novartis-provides-update-ruxcovid-study-ruxolitinib-hospitalized-patients-covid-19

46 SANOFI. Sanofi and Regeneron provide update on Kevzara® (sarilumab) phase 3 U.S. trial in COVID-19 patients, 2020. Available: https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00
47 Ramiro S, Mostard RLM, Magro-Checa C, *et al*. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the chiC study. *Ann Rheum Dis* 2020;79:1143–51.
48 Martínez-Urbistondo D, Costa Segovia R, Suárez Del Villar Carrero R, *et al*. Early combination of tocilizumab and corticosteroids: an upgrade in anti-inflammatory therapy for severe COVID. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa910. [Epub ahead of print: 04 Jul 2020].
49 Sanz Herrero F, Puchades Gimeno F, Ortega García P, *et al*. Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: an observational study. *J Intern Med* 2020. doi:10.1111/joim.13145. [Epub ahead of print: 30 Jun 2020].
50 Gupta S, Wang W, Hayek SS, *et al*. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med* 2021;181:41–51.
51 Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, *et al*. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. *Rheumatology* 2021;60:399–407.
52 De Luca G, Cavalli G, Campochiaro C, *et al*. Gm-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020;2:e465–73.
53 Temesgen Z, Assi M, Shweta FNU, *et al*. Gm-CSF neutralization with Lenzilumab in severe COVID-19 pneumonia: a case-cohort study. *Mayo Clin Proc* 2020;95:2382–94.
54 Annane D, Heming N, Grimaldi-Bensouda L, *et al*. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: a proof-of-concept study. *EClinicalMedicine* 2020;28:100590.
55 Della-Torre E, Campochiaro C, Cavalli G, *et al*. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann Rheum Dis* 2020;79:1277–85.
56 Laterre PF, François B, Collienne C, *et al*. Association of interleukin 7 immunotherapy with lymphocyte counts among patients with severe coronavirus disease 2019 (COVID-19). *JAMA Netw Open* 2020;3:e2016485.
57 Giudice V, Pagliano P, Vatrella A, *et al*. Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-Related acute respiratory distress syndrome: a controlled study. *Front Pharmacol* 2020;11:857.
58 D'Alessio A, Del Poggio P, Bracchi F, *et al*. Low-dose ruxolitinib plus steroid in severe SARS-CoV-2 pneumonia. *Leukemia* 2020:1–4.
59 Galvez-Romero JL, Palmeros-Rojas O, Real-Ramírez FA, *et al*. Cyclosporine a plus low-dose steroid treatment in COVID-19 improves clinical outcomes in patients with moderate to severe disease. A pilot study. *J Intern Med* 2020. doi:10.1111/joim.13223. [Epub ahead of print: 03 Dec 2020].
60 Mahase E. Covid-19: anti-TNF drug adalimumab to be trialled for patients in the community. *BMJ* 2020;371:m3847.
61 Bozzi G, Mangioni D, Minoia F, *et al*. Anakinra combined with methylprednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: an observational cohort study. *J Allergy Clin Immunol* 2020. doi:10.1016/j.jaci.2020.11.006. [Epub ahead of print: 19 Nov 2020].
62 Ucciferri C, Auricchio A, Di Nicola M, *et al*. Canakinumab in a subgroup of patients with COVID-19. *Lancet Rheumatol* 2020;2:e457–8.
63 Caracciolo M, Macheda S, Labate D, *et al*. Case report: canakinumab for the treatment of a patient with COVID-19 acute respiratory distress syndrome. *Front Immunol* 2020;11:1942.
64 Zelek WM, Cole J, Ponsford MJ, *et al*. Complement inhibition with the C5 blocker LFG316 in severe COVID-19. *Am J Respir Crit Care Med* 2020;202:1304–8.
65 Caballero A, Filgueira LM, Betancourt J, *et al*. Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab. *Clin Transl Immunology* 2020;9:e1218.
66 Mitjà O, Corbacho-Monné M, Ubals M, *et al*. Hydroxychloroquine for early treatment of adults with mild Covid-19: a Randomized-Controlled trial. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa1009. [Epub ahead of print: 16 Jul 2020].
67 Skipper CP, Pastick KA, Engen NW, *et al*. Hydroxychloroquine in nonhospitalized adults with early COVID-19 : a randomized trial. *Ann Intern Med* 2020;173:623–31.
68 Omrani AS, Pathan SA, Thomas SA, *et al*. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. *EClinicalMedicine* 2020;29:100645.
69 Wang M, Zhao Y, Hu W, *et al*. Treatment of COVID-19 patients with prolonged Post-Symptomatic viral shedding with leflunomide -- a single-center, randomized, controlled clinical trial. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa1417. [Epub ahead of print: 21 Sep 2020].
70 Hu K, Wang M, Zhao Y, *et al*. A small-scale medication of leflunomide as a treatment of COVID-19 in an open-label Blank-Controlled clinical trial. *Virol Sin* 2020;35:725–33.
71 Wang B, Li D, Liu T, *et al*. Subcutaneous injection of IFN alpha-2b for COVID-19: an observational study. *BMC Infect Dis* 2020;20:723.
72 Fu W, Liu Y, Liu L, *et al*. An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. *EClinicalMedicine* 2020;27:100547.
73 Cantini F, Niccoli L, Matarrese D, *et al*. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. *J Infect* 2020;81:318–56.
74 Bronte V, Ugel S, Tinazzi E. Baricitinib restrains the immune dysregulation in severe COVID-19 patients. *J Clin Invest*2020;130:6409–16.
75 Zhao H, Zhu Q, Zhang C, *et al*. Tocilizumab combined with favipiravir in the treatment of COVID-19: a multicenter trial in a small sample size. *Biomed Pharmacother* 2021;133:110825.
76 Parr JB. Time to reassess tocilizumab's role in COVID-19 pneumonia. *JAMA Intern Med* 2021;181:12.
77 Marshall JC, Murthy S, Diaz J, *et al*. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020;20:e192–7.
78 Lyngbakken MN, Berdal J-E, Eskesen A, *et al*. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. *Nat Commun* 2020;11:5284.

Immunomodulatory therapies for COVID-19 from the rheumatology perspective: a systematic literature review to inform EULAR points to consider

Online Supplementary Material

Table of Contents

Alunno A, *et al. Ann Rheum Dis* 2021;0:1–13. doi: 10.1136/annrheumdis-2020-219725

Alunno A, *et al. Ann Rheum Dis* 2021;0:1–13. doi: 10.1136/annrheumdis-2020-219725

Online Supplementary Text S1: Search strategy for pathophysiology of COVID-19

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to November 2, 2020>

Search Strategy: Covid & Pathophysiology

---

1 exp T-Lymphocytes/ (45024)
2 ((T adj2 lymphocyte*) or (T adj2 cell*) or Thymus Dependent Lymphocyte*).mp(106985)
3 exp B-Lymphocytes/ (10564)
4 ((b adj2 cell*) or (b adj2 lymphocyte*)).mp(50718)
5 B10.mp(463)
6 exp Biomarkers/ (176995)
7 (((biological or biochemical or biologic or immune or immunologic* or laboratory or surrogate or viral) adj3 marker*) or biomarker*).mp(250594)
8 exp Biopsy/ (40157)
9 (biopsy or biopsies).mp(114651)
10 B-Lymphocytes, Regulatory/ (374)
11 (breg* or "regulatory b cell*" or "regulatory b lymphocyte*").mp(1099)
12 exp Bronchoalveolar Lavage/ (3837)
13 ((Bronchoalveolar or bronchial or bronchopulmonary or Bronchioalveolar or lung or pulmonary) adj2 (lavage or wash*)).mp(8720)
14 (CD16 or FCgammaRIII or (IgG adj receptor*)).mp(1978)
15 Receptors, IgG/ (1403)
16 Antigens, CD19/ (882)
17 CD19.mp(3752)
18 CD4 Antigens/ (930)
19 CD4.mp(38856)
20 CD8 Antigens/ (525)
21 CD8.mp(24487)
22 exp Chemokines/ (13572)
23 (chemokine* or chemotactic* or intercrine*).mp(30771)
24 exp Complement System Proteins/ (4896)
25 complement.mp(31082)
26 exp Cytokines/ (120609)
27 (cytokine* or interleukin*).mp(171683)
28 exp Dendritic Cells/ (8077)
29 (((dendritic or interdigitating) adj2 cell*) or DC).mp(34118)
30 exp Endothelial Cells/ (18959)
31 ((endothelial or endothelium) adj2 cell*).mp(45902)
32 ((endothelial or endothelium) adj3 microparticle*).mp(291)
33 exp Endothelium/ (9505)
34 endothelium.mp(18957)
35 Eosinophils/ (2610)
36 eosinophil*.mp(17889)
37 exp T-Lymphocytes, Helper-Inducer/ (8679)
38 "T helper cell*".mp(2113)
39 exp Fibroblasts/ (27166)
40 fibroblast*.mp(53774)
41 exp Genes/ (100804)
42 (gene or genes).mp(755066)
43 exp Genome/ (155426)

44 genome*.mp(188459)
45 Genome-Wide Association Study/ (13155)
46 (GWAS or "GWA stud*" or "genome wide association stud*").mp(21707)
47 exp Hemostasis/ (9820)
48 (hemostasis or haemostasis).mp(10313)
49 exp Histology/ (33687)
50 (histology or histologic*).mp(167555)
51 ((immune or immunocompotent or immunocompetent) adj2 cell*).mp(40241)
52 exp Immune System/ (138423)
53 "immune system*".mp(44449)
54 exp Immunoglobulins/ (106188)
55 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*).mp(50150)
56 Immunosenescence/ (275)
57 (Immunosenescence or immunosenescense or immunosenesence).mp(1099)
58 exp Interferon Type I/ (6119)
59 Interferon-gamma/ (7582)
60 exp Interferons/ (15621)
61 interferon*.mp(40965)
62 exp Lymphocytes/ (63730)
63 lymphocyte*.mp(97245)
64 exp Macrophages/ (32803)
65 (macrophage* or histiocyte*).mp(71015)
66 Mast Cells/ (2767)
67 ("mast cell*" or mastocyte*).mp(7573)
68 exp MicroRNAs/ (41135)
69 (microRNA* or "micro RNA*" or miRNA* or mi-RNA* or miRs).mp(71821)
70 exp Monocytes/ (8102)
71 monocyte*.mp(27872)
72 exp Nasal Lavage/ (237)
73 ((nasal or nasopharingeal or nasopharyngeal or nose or nasopharynx) adj3 (lavage or irrigation or aspirate* or swab* or wash* or smear* or mucosa)).mp(7261)
74 exp Killer Cells, Natural/ (5220)
75 ("natural killer*" or "NK cell*" or NK).mp(16729)
76 Neutrophils/ (10439)
77 (neutrophil* or granulocyte*).mp(47471)
78 (oropharyngeal adj3 swab*).mp(438)
79 exp Leukocytes, Mononuclear/ (74463)
80 ("peripheral blood mononuclear cell*" or PBMC or (mononuclear adj2 leukocyte*)).mp(15035)
81 exp Plasma/ (4915)
82 (plasma or plasm).mp(193969)
83 Blood Platelets/ (7226)
84 (platelet* or thrombocyte*).mp(55469)
85 B-Lymphocytes, Regulatory/ (374)
86 T-Lymphocytes, Regulatory/ (6849)
87 Saliva/ (6472)
88 (saliva or spittle).mp(15463)
89 exp Serum/ (3019)
90 serum.mp(232308)
91 Sputum/ (2801)

92 (sputum or expectorate).mp(8692)
93 exp Feces/ (16049)
94 (stool* or faeces or feces).mp(32801)
95 exp Superantigens/ (258)
96 Superantigen*.mp(670)
97 exp T-Lymphocytes, Helper-Inducer/ (8679)
98 ("t helper*" or "helper cell*").mp(7829)
99 Th1 Cells/ (2976)
100 Th1.mp(11045)
101 Th17 Cells/ (3538)
102 Th17.mp(8665)
103 Th2 Cells/ (2677)
104 Th2.mp(9688)
105 Th22.mp(356)
106 Th9.mp(429)
107 exp Thrombosis/ (15110)
108 (thrombosis or thrombus or "blood clot*" or thrombotic).mp(54227)
109 T-Lymphocytes, Regulatory/ (6849)
110 (Treg or "t reg*" or (regulatory adj3 (lymphocyte* or cell*))).mp(20216)
111 Urine/ (2116)
112 urine.mp(55328)
113 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 (2075821)
114 exp Coronavirus/ (19595)
115 exp Coronavirus Infections/ (20991)
116 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (38713)
117 "severe acute respiratory syndrome*".ti,ab,kw,kf. (6855)
118 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1388)
119 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (28750)
120 114 or 115 or 116 or 117 or 118 or 119 (51103)
121 113 and 120 (12309)
122 limit 121 to yr="2019 -Current" (7539)

Embase

Database: Embase <1996 to November 2, 2020>
Search Strategy: Covid & Pathogenesis

---

1 exp t lymphocyte/ (456309)

2 ((T adj2 lymphocyte*) or (T adj2 cell*) or Thymus Dependent Lymphocyte*).mp. (591269)
3 exp b lymphocyte/ (147673)
4 ((b adj2 cell*) or (b adj2 lymphocyte*)).mp. (249121)
5 B10.mp. (2059)
6 biological marker/ (307140)
7 (((biological or biochemical or biologic or immune or immunologic* or laboratory or surrogate or viral) adj3 marker*) or biomarker*).mp. (578923)
8 exp biopsy/ (669360)
9 (biopsy or biopsies).mp. (771743)
10 regulatory b lymphocyte/ (960)
11 (breg* or "regulatory b cell*" or "regulatory b lymphocyte*").mp. (3888)
12 lung lavage/ (45132)
13 ((Bronchoalveolar or bronchial or bronchopulmonary or Bronchioalveolar or lung or pulmonary) adj2 (lavage or wash*)).mp. (58261)
14 CD16 antigen/ (8740)
15 (CD16 or FCgammaRIII or (IgG adj receptor*)).mp. (15723)
16 CD19 antigen/ (15516)
17 CD19.mp. (28635)
18 CD4 antigen/ (112927)
19 CD4.mp. (254302)
20 CD8.mp. (153758)
21 CD8 antigen/ (67128)
22 exp chemokine/ (215856)
23 (chemokine* or chemotactic* or intercrine*).mp. (193870)
24 exp complement/ (45769)
25 complement.mp. (140206)
26 exp cytokine/ (1380226)
27 (cytokine* or interleukin*).mp. (919536)
28 exp dendritic cell/ (100167)
29 (((dendritic or interdigitating) adj2 cell*) or DC).mp. (173804)
30 exp endothelium cell/ (170061)
31 ((endothelial or endothelium) adj2 cell*).mp. (238200)
32 endothelial microparticle/ (1283)
33 ((endothelial or endothelium) adj3 microparticle*).mp. (1755)
34 endothelial progenitor cell/ (9075)
35 exp endothelium/ (110181)
36 endothelium.mp. (243355)
37 eosinophil/ (40827)
38 Eosinophil*.mp. (104859)
39 exp helper cell/ (90736)
40 "T helper cell*".mp. (10123)
41 exp fibroblast/ (123146)
42 fibroblast*.mp. (266122)
43 exp gene/ (961112)
44 (gene or genes).mp. (3400074)
45 exp genome/ (273762)
46 genome*.mp. (548669)
47 genome-wide association study/ (24143)
48 (GWAS or "GWA stud*" or "genome wide association stud*").mp. (52611)
49 hemostasis/ (63878)
50 (hemostasis or haemostasis).mp. (80520)

51 exp histology/ (886402)
52 (histology or histologic*).mp. (771484)
53 immunocompetent cell/ (66110)
54 ((immune or immunocompotent or immunocompetent) adj2 cell*).mp. (148896)
55 exp immune system/ (1684358)
56 "immune system*".mp. (165426)
57 exp immunoglobulin/ (373027)
58 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*).mp. (568468)
59 immunosenescence/ (1384)
60 (Immunosenescence or immunosenescense or immunosenesence).mp. (3342)
61 exp interferon/ (499113)
62 interferon*.mp. (339214)
63 exp lymphocyte/ (674815)
64 lymphocyte*.mp. (753344)
65 exp macrophage/ (224069)
66 (macrophage* or histiocyte*).mp. (362232)
67 exp mast cell/ (33055)
68 ("mast cell*" or mastocyte*).mp. (44865)
69 exp microRNA/ (160021)
70 (microRNA* or "micro RNA*" or miRNA* or mi-RNA* or miRs).mp. (170200)
71 exp monocyte/ (96637)
72 monocyte*.mp. (177960)
73 nose smear/ (6102)
74 ((nasal or nasopharingeal or nasopharyngeal or nose or nasopharynx) adj3 (lavage or irrigation or aspirate* or swab* or wash* or smear* or mucosa)).mp. (29983)
75 natural killer cell/ (63740)
76 ("natural killer*" or "NK cell*" or NK).mp. (98324)
77 neutrophil/ (109021)
78 (neutrophil* or granulocyte*).mp. (328852)
79 (oropharyngeal adj3 swab*).mp. (1038)
80 peripheral blood mononuclear cell/ (67396)
81 ("peripheral blood mononuclear cell*" or PBMC or (mononuclear adj2 leukocyte*)).mp. (87892)
82 exp plasma/ (142187)
83 (plasma or plasm).mp. (893214)
84 platelet microparticle/ (1568)
85 exp thrombocyte/ (79775)
86 (platelet* or thrombocyte*).mp. (331188)
87 regulatory b lymphocyte/ (960)
88 regulatory t lymphocyte/ (65724)
89 saliva/ (25032)
90 (saliva or spittle).mp. (55943)
91 exp serum/ (158337)
92 serum.mp. (1046723)
93 sputum/ (19808)
94 (sputum or expectorate).mp. (53160)
95 feces/ (43635)
96 (stool* or faeces or feces).mp. (154107)
97 superantigen/ (3561)
98 superantigen*.mp. (5363)

99 exp helper cell/ (90736)
100 ("t helper*" or "helper cell*").mp. (46692)
101 Th1.mp. (68879)
102 Th17.mp. (34832)
103 Th2.mp. (61592)
104 Th22.mp. (1216)
105 Th9.mp. (1345)
106 exp thrombosis/ (276774)
107 (thrombosis or thrombus or "blood clot*" or thrombotic).mp. (482680)
108 regulatory t lymphocyte/ (65724)
109 (Treg or "t reg*" or (regulatory adj3 (lymphocyte* or cell*))).mp. (92424)
110 urine/ (65124)
111 urine.mp. (352699)
112 nasal lavage/ (1514)
113 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 (9203624)
114 exp Coronavirinae/ (16754)
115 exp Coronavirus infection/ (17958)
116 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (35694)
117 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (1168)
118 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (37658)
119 "severe acute respiratory syndrome*".ti,ab,kw. (9296)
120 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (33830)
121 114 or 115 or 116 or 117 or 118 or 119 or 120 (64189)
122 113 and 121 (20125)
123 limit 122 to yr="2019 -Current" (10224)

CINAHL
8/10/2020
S106 S96 AND S104 S105 S96 AND S104 S104 S103 S97 OR S98 OR S99 OR S100 OR S101OR S102 OR S103 (MH "Coronavirus+") S102 S101 "severe acute respiratory syndrome*" ("2019nCoV*" or 2019nCoV* or "19nCoV*" or 19nCoV* or nCoV2019* or "nCoV2019*" or nCoV19* or "nCoV-19*" or "COVID19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "ncov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARSCoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARSCov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or

SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARScoronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus2*" or "SARS coronovirus2*" or covid)
S100 (coronavirus* or coronovirus* or coronavirinae* or CoV)
S99 ((corona* or corono*) N1 (virus* or viral*or virinae*)).
S98 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").
S97 (MH "Coronavirus Infections+")
S96 S1 OR S12 OR S23OR S34 OR S45 OR S56 OR S67 OR S78 OR S89 OR S12 OR S23 OR S34 OR S45 OR S56 OR S67 OR S78 OR S89 OR S10 OR S11 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95
S95 neutrophil* or granulocyte*
S94 urine
S93 TH9
S92 sputum or expectorate
S91 "mast cell*" or mastocyte"
S90 macrophage* or histiocyte*
S89 (MH "Eosinophils")
S88 ((dendritic or interdigitating) N2 cell*) or DC
S87 (MH "Chemokines+")
S86 (MH "Urine")
S85 Treg or "t reg*" or (regulatory N3 (lymphocyte* or cell*))
S84 thrombosis or thrombus or "blood clot*" or thrombotic
S83 (MH "Thrombosis+")
S82 Th22
S81 Th17
S80 Th2
S79 Th1
S78 (MH "Bronchoalveolar Lavage")
S77 "t helper*" or "helper cell*"
S76 (MH "Dendritic Cells")
S75 Superantigen*
S74 CD8
S73 (stool* or faeces or feces)
S72 (MH "Feces")
S71 (MH "Sputum")
S70 serum
S69 (MH "Serum")
S68 saliva or spittle
S67 endothelium
S66 (MH "Saliva")
S65 platelet* or thrombocyte*
S64 cytokine* or interleukin*
S63 (MH "Blood Platelets")
S62 plasma or plasm
S61 CD4

S60 (MH "Plasma")
S59 "peripheral blood mononuclear cell*" or PBMC or (mononuclear N2 leukocyte*)
S58 (MH "Leukocytes, Mononuclear+")
S57 oropharyngeal N3 swab*
S56 (MH "Endothelium")
S55 (MH "Neutrophils")
S54 "natural killer*" or "NK cell*" or NK
S53 (MH "Killer Cells, Natural")
S52 (MH "Cytokines")
S51 (nasal or nasopharingeal or nasopharyngeal or nose or nasopharynx) N3 (lavage or irrigation or aspirate* or swab* or wash* or smear* or mucosa)
S50 (MH "Nasal Lavage")
S49 monocyte*
S48 CD19
S47 (MH "Monocytes")
S46 microRNA* or "micro RNA*" or miRNA* or mi-RNA* or miRs
S45 (endothelial or endothelium) N3 microparticle*
S44 (MH "MicroRNA")
S43 (MH "Mast Cells")
S42 (MH "Macrophages+")
S41 lymphocyte*
S40 complement
S39 (MH "Lymphocytes+")
S38 Interferon*
S37 (MH "Interferons")
S36 Immunosenescence or immunosenescense or immunosenesence
S35 CD16 or FCgammaRIII or (IgG N receptor*)
S34 chemokine* or chemotactic* or intercrine*
S33 Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*
S32 (MH "Immunoglobulins+")
S31 "immune system*"
S30 (MH "Immune System+")
S29 (immune or immunocompotent or immunocompetent) N2 cell*
S28 breg* or "regulatory b cell*" or "regulatory b lymphocyte*"
S27 histology or histologic*
S26 (MH "Histology")
S25 hemostasis or haemostasis
S24 (MH "Hemostasis+")
S23 (endothelial or endothelium) N2 cell*
S22 GWAS or "GWA stud*" or "genome wide association stud*"
S21 (Bronchoalveolar or bronchial or bronchopulmonary or Bronchioalveolar or lung or pulmonary)
N2 (lavage or wash*)
S20 (MH "Genome Wide Association Study")
S19 genome*
S18 (MH "Genome+")
S17gene or genes
S16 (MH "Complement")
S15 (MH "Genes+")
S14 fibroblast*

S13 (MH "Fibroblasts+")
S12 (MH "Endothelial Cells")
S11 "T helper cell*"
S10 eosinophil*
S9 biopsy or biopsies
S8 (MH "Biopsy")
S7 ((biological or biochemical or biologic or immune or immunologic* or laboratory or surrogate or viral) N3 marker*) or biomarker*
S6 (MH "Biological Markers+")
S5 B10
S4 (b N2 cell*) or (b N2 lymphocyte*)
S3 (MH "B Lymphocytes")
S2 (T N2 lymphocyte*) or (T N2 cell*) or (Thymus Dependent Lymphocyte*)
S1 (MH "T Lymphocytes+")

The Cochrane Library

November 2, 2020

ID	Search Hits
#1	MeSH descriptor: [T-Lymphocytes] explode all trees 3317
#2	((T near/2 lymphocyte*) or (T near/2 cell*) or (Thymus Dependent Lymphocyte*)):ti,ab,kw 13935
#3	MeSH descriptor: [B-Lymphocytes] explode all trees 491
#4	((b near/2 cell*) or (b near/2 lymphocyte*)):ti,ab,kw 6336
#5	(B10):ti,ab,kw 56
#6	MeSH descriptor: [Biomarkers] explode all trees 19928
#7	(((biological or biochemical or biologic or immune or immunologic or laboratory or surrogate or viral) near/3 marker*) or biomarker*):ti,ab,kw 43143
#8	MeSH descriptor: [Biopsy] explode all trees 5629
#9	(biopsy or biopsies):ti,ab,kw 28898
#10	MeSH descriptor: [B-Lymphocytes, Regulatory] explode all trees 3
#11	(breg* or "regulatory b cell*" or "regulatory b lymphocyte*"):ti,ab,kw 63
#12	MeSH descriptor: [Bronchoalveolar Lavage] explode all trees 543
#13	((Bronchoalveolar or bronchial or bronchopulmonary or Bronchioalveolar or lung or pulmonary) near/2 (lavage or wash*)):ti,ab,kw 1429
#14	(CD16 or FCgammaRIII or (IgG adj receptor*)):ti,ab,kw 510
#15	MeSH descriptor: [Receptors, IgG] explode all trees 101
#16	(CD19):ti,ab,kw 766
#17	MeSH descriptor: [Antigens, CD19] explode all trees 34
#18	MeSH descriptor: [CD4 Antigens] explode all trees 169
#19	(CD4):ti,ab,kw 10970
#20	MeSH descriptor: [CD8 Antigens] explode all trees 69
#21	(CD8):ti,ab,kw 4437
#22	MeSH descriptor: [Chemokines] explode all trees 1598
#23	(chemokine* or chemotactic* or intercrine*):ti,ab,kw 2610
#24	MeSH descriptor: [Complement System Proteins] explode all trees 699
#25	(complement):ti,ab,kw 4639
#26	MeSH descriptor: [Cytokines] explode all trees 20089
#27	(cytokine* or interleukin*):ti,ab,kw 29474
#28	MeSH descriptor: [Dendritic Cells] explode all trees 268

#29 (((dendritic or interdigitating) near/2 cell*) or DC):ti,ab,kw 4416
#30 MeSH descriptor: [Endothelial Cells] explode all trees 379
#31 ((endothelial or endothelium) near/2 cell*):ti,ab,kw 3779
#32 ((endothelial or endothelium) near/3 microparticle*):ti,ab,kw 105
#33 MeSH descriptor: [Endothelial Progenitor Cells] explode all trees 78
#34 MeSH descriptor: [Endothelium] explode all trees 3109
#35 (endothelium):ti,ab,kw 6396
#36 MeSH descriptor: [Eosinophils] explode all trees 783
#37 (Eosinophil*):ti,ab,kw 4818
#38 MeSH descriptor: [T-Lymphocytes, Helper-Inducer] explode all trees 468
#39 ("T helper cell*"):ti,ab,kw 129
#40 MeSH descriptor: [Fibroblasts] explode all trees 253
#41 (fibroblast*):ti,ab,kw 2526
#42 MeSH descriptor: [Genes] explode all trees 1581
#43 (gene*):ti,ab,kw 212810
#44 MeSH descriptor: [Genome] explode all trees 1944
#45 (genome*):ti,ab,kw 2427
#46 MeSH descriptor: [Genome-Wide Association Study] explode all trees 129
#47 (GWAS or "GWA stud*" or "genome wide association stud*"):ti,ab,kw 313
#48 MeSH descriptor: [Hemostasis] explode all trees 4848
#49 (hemostasis or haemostasis):ti,ab,kw 5675
#50 MeSH descriptor: [Histology] explode all trees 1337
#51 (histology or histologic*):ti,ab,kw 28746
#52 ((immune or immunocompotent) near/2 cell*):ti,ab,kw 3654
#53 MeSH descriptor: [Immune System] explode all trees 11878
#54 ("immune system*"):ti,ab,kw 5140
#55 MeSH descriptor: [Immunoglobulins] explode all trees 25489
#56 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*):ti,ab,kw 13773
#57 MeSH descriptor: [Immunosenescence] explode all trees 2
#58 (Immunosenescence or immunosenescense or immunosenesence):ti,ab,kw 104
#59 MeSH descriptor: [Interferon Type I] explode all trees 4393
#60 MeSH descriptor: [Interferon-gamma] explode all trees 1074
#61 MeSH descriptor: [Interferons] explode all trees 5775
#62 (interferon*):ti,ab,kw 15371
#63 MeSH descriptor: [Lymphocytes] explode all trees 5186
#64 (Lymphocyte*):ti,ab,kw 19255
#65 MeSH descriptor: [Macrophages] explode all trees 492
#66 (macrophage* or histiocyte*):ti,ab,kw 4190
#67 MeSH descriptor: [Mast Cells] explode all trees 207
#68 ("mast cell*" or mastocyte*):ti,ab,kw 809
#69 MeSH descriptor: [MicroRNAs] explode all trees 153
#70 (microRNA* or "micro RNA*" or miRNA* or mi-RNA* or miRs):ti,ab,kw 972
#71 MeSH descriptor: [Monocytes] explode all trees 748
#72 (monocyte*):ti,ab,kw 4118
#73 MeSH descriptor: [Nasal Lavage] explode all trees 255
#74 ((nasal or nasopharingeal or nasopharyngeal or nose or nasopharynx) near/3 (lavage or irrigation or aspirate* or swab* or wash* or smear* or mucosa)):ti,ab,kw 3181
#75 MeSH descriptor: [Killer Cells, Natural] explode all trees 764
#76 ("natural killer*" or "NK cell*" or NK):ti,ab,kw 3035
#77 MeSH descriptor: [Neutrophils] explode all trees 1367

#78 (neutrophil* or granulocyte*):ti,ab,kw 15333
#79 (oropharyngeal near/3 swab*):ti,ab,kw 80
#80 MeSH descriptor: [Leukocytes, Mononuclear] explode all trees 6605
#81 ("peripheral blood mononuclear cell*" or PBMC or (mononuclear near/2 leukocyte*)):ti,ab,kw 2901
#82 MeSH descriptor: [Plasma] explode all trees 972
#83 (plasma or plasm):ti,ab,kw 96931
#84 MeSH descriptor: [Blood Platelets] explode all trees 1961
#85 (platelet* or thrombocyte*):ti,ab,kw 28701
#86 MeSH descriptor: [B-Lymphocytes, Regulatory] explode all trees 3
#87 MeSH descriptor: [T-Lymphocytes, Regulatory] explode all trees 274
#88 MeSH descriptor: [Saliva] explode all trees 2652
#89 (saliva or spittle):ti,ab,kw 7069
#90 MeSH descriptor: [Serum] explode all trees 868
#91 (serum):ti,ab,kw 98631
#92 MeSH descriptor: [Sputum] explode all trees 1262
#93 (sputum or expectorate):ti,ab,kw 5882
#94 MeSH descriptor: [Feces] explode all trees 2833
#95 ((stool* or faeces or feces)):ti,ab,kw 13931
#96 MeSH descriptor: [Superantigens] explode all trees 11
#97 (Superantigen*):ti,ab,kw 41
#98 ("t helper*" or "helper cell*"):ti,ab,kw 902
#99 (Th1):ti,ab,kw 1310
#100 (Th17):ti,ab,kw 486
#101 (Th2):ti,ab,kw 1353
#102 (Th22):ti,ab,kw 50
#103 (Th9):ti,ab,kw 23
#104 MeSH descriptor: [Thrombosis] explode all trees 4754
#105 (thrombosis or thrombus or "blood clot*" or thrombotic):ti,ab,kw 21776
#106 MeSH descriptor: [T-Lymphocytes, Regulatory] explode all trees 274
#107 (Treg or "t reg*" or (regulatory near/3 (lymphocyte* or cell*))):ti,ab,kw 1663
#108 MeSH descriptor: [Urine] explode all trees 641
#109 (Urine):ti,ab,kw 40231
#110 {or #1-#109} 549437
#111 MeSH descriptor: [Coronavirus] explode all trees 35
#112 MeSH descriptor: [Coronavirus Infections] explode all trees 297
#113 (((corona* or corono*) near/1 (virus* or viral* or virinae*))):ti,ab,kw 52
#114 ((coronavirus* or coronovirus* or coronavirinae* or CoV)):ti,ab,kw 727
#115 (("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid)):ti,ab,kw 1106
#116 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes") 373
#117 {or #111-#116} 1345
#118 #110 and #117 619
#119 #118 with Publication Year from 2019 to present, in Trials 499

Online Supplementary Text S2: Search strategy for COVID-19 treatment

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to week 50, 2020>

Search Strategy: Covid & Therapy

---

1 Abatacept/ (579)
2 (Abatacept or "CTLA4 Ig" or "CTLA4 immunoglobulin" or orencia).mp. (1197)
3 ABX464.mp. dentifier, synonyms] (7)
4 Adalimumab/ (2026)
5 (Adalimumab or adaly or amgevita or amjevita or humira or imraldi or trudexa).mp. dentifier, synonyms] (4179)
6 Interleukin 1 Receptor Antagonist Protein/ (863)
7 (Anakinra or kineret or "recombinant interleukin 1 receptor antagonist" or "recombinant interleukin 1 receptor blocker" or "recombinant interleukin 1 receptor blocking agent").mp. dentifier, synonyms] (882)
8 ARGX-117.mp. dentifier, synonyms] (0)
9 avdoralimab.mp. dentifier, synonyms] (0)
10 Azathioprine/ (1087)
11 (Azathioprine or arathioprin or arathioprine or immurel or imurel).mp. dentifier, synonyms] (3327)
12 (Baricitinib or olumiant).mp. dentifier, synonyms] (356)
13 BDB-001.mp. dentifier, synonyms] (0)
14 Bevacizumab/ (3553)
15 (Bevacizumab or avastin).mp. dentifier, synonyms] (7906)
16 Brensocatib.mp. dentifier, synonyms] (0)
17 (Canakinumab or ilaris).mp. dentifier, synonyms] (492)
18 exp "Cell- and Tissue-Based Therapy"/ (42360)
19 ("cell based therapy" or "cell based therapies" or "cell therapy" or "cell therapies" or "cellular therapy" or "cellular therapies").mp. dentifier, synonyms] (17559)
20 Certolizumab.mp. dentifier, synonyms] (714)
21 exp Chloroquine/ (2273)
22 Chloroquin*.mp. dentifier, synonyms] (4346)
23 CIGB-258.mp. dentifier, synonyms] (0)
24 CMAB806.mp. dentifier, synonyms] (0)
25 exp Colchicine/ (886)
26 Colchicine.mp. dentifier, synonyms] (2730)
27 exp Adrenal Cortex Hormones/ (38366)
28 (corticosteroid* or "adrenal cortex hormone*" or "cortical steroid*" or "cortico steroid*" or corticoid* or "corticosteroid agent*").mp. dentifier, synonyms] (29383)
29 exp Cyclosporins/ (2310)
30 Cyclosporin*.mp. dentifier, synonyms] (6643)
31 CYT-107.mp. dentifier, synonyms] (0)
32 exp Dexamethasone/ (5326)
33 Dexamethasone.mp. dentifier, synonyms] (12801)
34 DFV890.mp. dentifier, synonyms] (0)
35 Ebastine.mp. dentifier, synonyms] (72)
36 Eculizumab.mp. dentifier, synonyms] (1052)
37 Etanercept/ (1273)
38 (Etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor Fc fusion protein" or "tumour necrosis factor receptor Fc fusion protein").mp. dentifier, synonyms] (2787)

39 Fedratinib.mp. dentifier, synonyms] (61)
40 Filgotinib.mp. dentifier, synonyms] (87)
41 Fingolimod Hydrochloride/ (720)
42 (Fingolimod or gilenia or gilenya).mp. dentifier, synonyms] (1398)
43 (Golimumab or simponi).mp. dentifier, synonyms] (805)
44 (Guselkumab or tremfya).mp. dentifier, synonyms] (234)
45 exp Glucocorticoids/ (21083)
46 glucocorticoid*.mp. dentifier, synonyms] (22665)
47 HCR040.mp. dentifier, synonyms] (0)
48 Hydroxychloroquine/ (1171)
49 (Hydroxychloroquine or plaquenil).mp. dentifier, synonyms] (3003)
50 IFX-1.mp. dentifier, synonyms] (14)
51 Imatinib Mesylate/ (1814)
52 (Imatinib or gleevac or gleevec or glivec).mp. dentifier, synonyms] (4620)
53 exp Immunoglobulins/ (106188)
54 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*).mp. dentifier, synonyms] (50150)
55 exp Immunotherapy/ (44172)
56 (Immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or "BRM therap*" or "immune therap*" or "immunoglobulin therap*" or "immunological therap*" or "immunological treatment*" or "immunomodulatory intervention*").mp. dentifier, synonyms] (48544)
57 IMU-838.mp. dentifier, synonyms] (2)
58 Infliximab/ (2440)
59 (Infliximab or flixabi or inflectra or remicade or remsima or renflexis).mp. dentifier, synonyms] (5286)
60 exp Interferons/ (15621)
61 Interferon*.mp. dentifier, synonyms] (40965)
62 Itolizumab.mp. dentifier, synonyms] (28)
63 Immunoglobulins, Intravenous/ (2436)
64 IVIG.mp. dentifier, synonyms] (2567)
65 (Ixekizumab or taltz).mp. dentifier, synonyms] (510)
66 Jakotinib.mp. dentifier, synonyms] (0)
67 Leflunomide/ (240)
68 (Leflunomide or arava).mp. dentifier, synonyms] (695)
69 Masitinib.mp. dentifier, synonyms] (63)
70 Mast Cells/ (2767)
71 ((mast adj cell*) or mastocyte*).mp. dentifier, synonyms] (7573)
72 Mavrilimumab.mp. dentifier, synonyms] (19)
73 Methotrexate/ (4535)
74 (Methotrexate or metoject or nordimet or novatrex).mp. dentifier, synonyms] (10851)
75 exp Methylprednisolone/ (2121)
76 Methylprednisolone.mp. dentifier, synonyms] (4915)
77 Mycophenolic Acid/ (1248)
78 (Mycophenolate or (mycophenolic adj acid) or myfortic or (mycophenolate adj mofetil)).mp. dentifier, synonyms] (3724)
79 (Nintedanib or intedanib).mp. dentifier, synonyms] (766)
80 exp Anti-Inflammatory Agents, Non-Steroidal/ (24544)
81 (NSAID* or "non steroid anti inflammatory agent*" or "non steroid anti inflammatory drug*" or "non steroidal anti inflammatory agent*" or "non steroidal anti inflammatory drug*" or "nonsteroid antiinflammatory agent*" or "nonsteroid antiinflammatory drug*" or "nonsteroidal

antiinflammatory agent*" or "nonsteroidal antiinflammatory drug*" or "non steroid antiinflammatory agent*" or "non steroid antiinflammatory drug*" or "non steroidal antiinflammatory agent*" or "non steroidal antiinflammatory drug*" or "nonsteroid anti inflammatory agent*" or "nonsteroid anti inflammatory drug*" or "nonsteroidal anti inflammatory agent*" or "nonsteroidal anti inflammatory drug*").mp. dentifier, synonyms] (12245)
82 (Ocrelizumab or ocrevus).mp. dentifier, synonyms] (285)
83 Otilimab.mp. dentifier, synonyms] (2)
84 Programmed Cell Death 1 Receptor/ (4857)
85 (PD-1 or Gilvetmab or "programmed cell death 1 receptor").mp. dentifier, synonyms] (13078)
86 (Pembrolizumab or keytruda or lambrolizumab).mp. dentifier, synonyms] (4063)
87 exp Prednisolone/ (4716)
88 Prednisolone.mp. dentifier, synonyms] (7040)
89 Prednisone/ (3337)
90 Prednisone.mp. dentifier, synonyms] (7442)
91 (Ravulizumab or ultomiris).mp. dentifier, synonyms] (29)
92 ((recombinant adj2 "interleukin 2") or lymphocult).mp. dentifier, synonyms] (92)
93 (recombinant adj2 "interleukin 7").mp. dentifier, synonyms] (18)
94 Rituximab/ (4433)
95 (Rituximab or mabthera or truxima).mp. dentifier, synonyms] (10152)
96 (Ruxolitinib or jakafi or jakavi).mp. dentifier, synonyms] (1043)
97 (Sarilumab or kevzara).mp. dentifier, synonyms] (133)
98 (Secukinumab or cosentyx).mp. dentifier, synonyms] (1013)
99 Selinexor.mp. dentifier, synonyms] (163)
100 Siltuximab.mp. dentifier, synonyms] (88)
101 exp Stem Cells/ (56740)
102 "stem cell*".mp. dentifier, synonyms] (126152)
103 Sulfasalazine/ (376)
104 (Sulphasalazine or salazopyrine or sulfasalazine or salazosulfapyridine).mp. dentifier, synonyms] (1086)
105 TD-0903.mp. dentifier, synonyms] (0)
106 (Tocilizumab or roactemra).mp. dentifier, synonyms] (2307)
107 (Tranilast or rizaben).mp. dentifier, synonyms] (144)
108 ("tumor necrosis factor alpha inhibitor*" or "tumour necrosis factor alpha inhibitor*").mp. dentifier, synonyms] (517)
109 ("anti TNF agent*" or "anti TNF alpha agent*").mp. dentifier, synonyms] (834)
110 ("anti tumor necrosis factor agent*" or "anti tumour necrosis factor agent*").mp. dentifier, synonyms] (181)
111 ("TNF alpha inhibitor*" or "TNF inhibitor*").mp. dentifier, synonyms] (1775)
112 ("tumur necrosis factor inhibitor*" or "tumour necrosis factor inhibitor*").mp. dentifier, synonyms] (257)
113 (Upadacitinib or rinvoq).mp. dentifier, synonyms] (116)
114 (Ustekinumab or stelara).mp. dentifier, synonyms] (1401)
115 Ustekinumab/ (605)
116 Vafidemstat.mp. dentifier, synonyms] (1)
117 vMIP.mp. dentifier, synonyms] (20)
118 zilucoplan.mp. dentifier, synonyms] (4)
119 (acalabrutinib or "acp 196" or acp196 or calquence).mp. dentifier, synonyms] (141)
120 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or

70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 (506357)
121 exp Coronavirus/ (19595)
122 exp Coronavirus Infections/ (20991)
123 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (38713)
124 "severe acute respiratory syndrome*".ti,ab,kw,kf. (6855)
125 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1388)
126 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (28750)
127 121 or 122 or 123 or 124 or 125 or 126 (51103)
128 120 and 127 (5416)
129 limit 128 to yr="2019 -Current" (3615)

Embase
Database: Embase <1996 to week 50, 2020>
Search Strategy: Covid & Therapy
---
1 abatacept/ (9193)
2 (Abatacept or "CTLA4 Ig" or "CTLA4 immunoglobulin" or orencia).mp. (9964)
3 ABX464.mp. (17)
4 acalabrutinib/ (534)
5 (Acalabrutinib or "acp 196" or acp196 or calquence).mp. (569)
6 adalimumab/ (33496)
7 (Adalimumab or adaly or amgevita or amjevita or humira or imraldi or trudexa).mp. (34253)
8 anakinra/ (2412)
9 (Anakinra or kineret or "recombinant interleukin 1 receptor antagonist" or "recombinant interleukin 1 receptor blocker" or "recombinant interleukin 1 receptor blocking agent").mp. (8661)
10 ARGX-117.mp. (1)
11 avdoralimab.mp. (1)
12 azathioprine/ (71856)
13 (Azathioprine or arathioprin or arathioprine or immurel or imurel).mp. (73616)
14 baricitinib/ (1171)
15 (Baricitinib or olumiant).mp. (1215)
16 BDB-001.mp. (1)
17 bevacizumab/ (58063)
18 (Bevacizumab or avastin).mp. (59931)
19 brensocatib/ (2)
20 Brensocatib.mp. (2)
21 canakinumab/ (3040)
22 (Canakinumab or ilaris).mp. (3139)
23 exp cell therapy/ (202065)

24 ("cell based therapy" or "cell based therapies" or "cell therapy" or "cell therapies" or "cellular therapy" or "cellular therapies").mp. (68705)
25 Certolizumab.mp. (7209)
26 chloroquine/ (24968)
27 Chloroquin*.mp. (28360)
28 CIGB-258.mp. (0)
29 CMAB806.mp. (0)
30 exp colchicine/ (20097)
31 Colchicine.mp. (21834)
32 exp corticosteroid/ (713138)
33 (corticosteroid* or "adrenal cortex hormone*" or "cortical steroid*" or "cortico steroid*" or corticoid* or "corticosteroid agent*").mp. (254142)
34 cyclosporine/ (12119)
35 Cyclosporin*.mp. (128632)
36 CYT-107.mp. (25)
37 dexamethasone/ (116542)
38 Dexamethasone.mp. (125934)
39 DFV890.mp. (0)
40 ebastine/ (1148)
41 Ebastine.mp. (1181)
42 eculizumab/ (5141)
43 Eculizumab.mp. (5371)
44 etanercept/ (31276)
45 (Etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor Fc fusion protein" or "tumour necrosis factor receptor Fc fusion protein").mp. (32234)
46 fedratinib/ (398)
47 Fedratinib.mp. (413)
48 filgotinib/ (383)
49 Filgotinib.mp. (389)
50 fingolimod/ (9700)
51 (Fingolimod or gilenia or gilenya).mp. (9947)
52 golimumab/ (6880)
53 (Golimumab or simponi).mp. (7051)
54 guselkumab/ (692)
55 (Guselkumab or tremfya).mp. (720)
56 exp glucocorticoid/ (547889)
57 glucocorticoid*.mp. (109216)
58 HCR040.mp. (0)
59 hydroxychloroquine/ (23249)
60 (Hydroxychloroquine or plaquenil).mp. (24266)
61 IFX-1.mp. (95)
62 imatinib/ (41910)
63 (Imatinib or gleevac or gleevec or glivec).mp. (43723)
64 exp immunoglobulin/ (373027)
65 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*).mp. (568468)
66 exp immunotherapy/ (191127)
67 (Immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or "BRM therap*" or "immune therap*" or "immunoglobulin therap*" or "immunological therap*" or "immunological treatment*" or "immunomodulatory intervention*").mp. (182967)
68 IMU-838.mp. (8)

69 infliximab/ (50638)
70 (Infliximab or flixabi or inflectra or remicade or remsima or renflexis).mp. (51789)
71 exp interferon/ (499113)
72 Interferon*.mp. (339214)
73 itolizumab/ (77)
74 IVIG.mp. (16952)
75 ixekizumab/ (1706)
76 (Ixekizumab or taltz).mp. (1763)
77 Jakotinib.mp. (0)
78 leflunomide/ (11660)
79 (Leflunomide or arava).mp. (11973)
80 masitinib/ (507)
81 Masitinib.mp. (537)
82 mast cell/ (32134)
83 ((mast adj cell*) or mastocyte*).mp. (44865)
84 mavrilimumab/ (110)
85 Mavrilimumab.mp. (110)
86 methotrexate/ (138928)
87 (Methotrexate or metoject or nordimet or novatrex).mp. (142684)
88 methylprednisolone/ (78064)
89 Methylprednisolone.mp. (85801)
90 mycophenolic acid/ (17362)
91 (Mycophenolate or (mycophenolic adj acid) or myfortic or (mycophenolate adj mofetil)).mp. (68499)
92 nintedanib/ (3037)
93 (Nintedanib or intedanib).mp. (3252)
94 exp nonsteroid antiinflammatory agent/ (580879)
95 (NSAID* or "non steroid anti inflammatory agent*" or "non steroid anti inflammatory drug*" or "non steroidal anti inflammatory agent*" or "non steroidal anti inflammatory drug*" or "nonsteroid antiinflammatory agent*" or "nonsteroid antiinflammatory drug*" or "nonsteroidal antiinflammatory agent*" or "nonsteroidal antiinflammatory drug*" or "non steroid antiinflammatory agent*" or "non steroid antiinflammatory drug*" or "non steroidal antiinflammatory agent*" or "non steroidal antiinflammatory drug*" or "nonsteroid anti inflammatory agent*" or "nonsteroid anti inflammatory drug*" or "nonsteroidal anti inflammatory agent*" or "nonsteroidal anti inflammatory drug*").mp. (131423)
96 ocrelizumab/ (1735)
97 (Ocrelizumab or ocrevus).mp. (1805)
98 otilimab/ (17)
99 Otilimab.mp. (17)
100 gilvetmab/ (251)
101 (PD-1 or Gilvetmab).mp. (31251)
102 programmed cell death 1 receptor.mp. (221)
103 pembrolizumab/ (15300)
104 (Pembrolizumab or keytruda or lambrolizumab).mp. (16207)
105 prednisolone/ (97691)
106 Prednisolone.mp. (108112)
107 prednisone/ (127911)
108 Prednisone.mp. (132005)
109 ravulizumab/ (93)
110 (Ravulizumab or ultomiris).mp. (96)
111 exp recombinant interleukin 2/ (5784)

112 ((recombinant adj2 "interleukin 2") or lymphocult).mp. (4146)
113 exp recombinant interleukin 7/ (339)
114 (recombinant adj2 "interleukin 7").mp. (363)
115 rituximab/ (79475)
116 (Rituximab or mabthera or truxima).mp. (83435)
117 ruxolitinib/ (4756)
118 (Ruxolitinib or jakafi or jakavi).mp. (4910)
119 sarilumab/ (594)
120 (Sarilumab or kevzara).mp. (615)
121 secukinumab/ (3533)
122 (Secukinumab or cosentyx).mp. (3646)
123 selinexor/ (664)
124 Selinexor.mp. (699)
125 siltuximab/ (687)
126 Siltuximab.mp. (706)
127 exp stem cell/ (362533)
128 (Stem adj cell*).mp. (538786)
129 salazosulfapyridine/ (19864)
130 (Sulphasalazine or salazopyrine or sulfasalazine or salazosulfapyridine).mp. (20375)
131 TD-0903.mp. (1)
132 tocilizumab/ (12168)
133 (Tocilizumab or roactemra).mp. (12676)
134 tranilast/ (1181)
135 (Tranilast or rizaben).mp. (1222)
136 exp tumor necrosis factor inhibitor/ (90671)
137 ("tumor necrosis factor alpha inhibitor*" or "tumour necrosis factor alpha inhibitor*").mp. (6793)
138 ("anti TNF agent*" or "anti TNF alpha agent*").mp. (4699)
139 ("anti tumour necrosis factor agent*" or "anti tumor necrosis factor agent*").mp. (582)
140 ("TNF alpha inhibitor*" or "TNF inhibitor*").mp. (7426)
141 ("tumour necrosis factor inhibitor*" or "tumor necrosis factor inhibitor*").mp. (14939)
142 upadacitinib/ (408)
143 (Upadacitinib or rinvoq).mp. (417)
144 ustekinumab/ (7049)
145 (Ustekinumab or stelara).mp. (7247)
146 vafidemstat/ (6)
147 Vafidemstat.mp. (6)
148 vMIP.mp. (139)
149 zilucoplan/ (25)
150 zilucoplan.mp. (25)
151 itolizumab.mp. (81)
152 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 (3020762)

153 exp Coronavirinae/ (16754)
154 exp Coronavirus infection/ (17958)
155 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (35694)
156 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (1168)
157 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (37658)
158 "severe acute respiratory syndrome*".ti,ab,kw. (9296)
159 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (33830)
160 153 or 154 or 155 or 156 or 157 or 158 or 159 (64189)
161 152 and 160 (9143)
162 limit 161 to yr="2019 -Current" (5942)

CINAHL
09/12/2020
S125 S115 AND S123
S124 S115 AND S123
S123 S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122
S122 (MH "Coronavirus+")
S121 "severe acute respiratory syndrome*"
S120 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or"nCoV-19*" or "COVID-19*" or COVID19* or"COVID-2019*" orCOVID2019* or "HCoV-19*" or HCoV19* or"HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n- cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARSCoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or
SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or
covid)
S119 (coronavirus* or coronovirus* or coronavirinae* or CoV)
S118 ((corona* or corono*) N1 (virus* or viral* or virinae*)).
S117 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").S116 (MH "Coronavirus Infections+")
S115 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR
S11 OR S12 OR S13 OR
S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR
S20 OR S21 OR S22 OR
S23 OR S24 OR S25 OR
S26 OR S27 OR S28 OR
S29 OR S30 OR S31 OR
S32 OR S33 OR S34 OR
S35 OR S36 OR S37 OR

S38 OR S39 OR S40 OR
S41 OR S42 OR S43 OR
S44 OR S45 OR S46 OR
S47 OR S48 OR S49 OR
S50 OR S51 OR S52 OR
S53 OR S54 OR S55 OR
S56 OR S57 OR S58 OR
S59 OR S60 OR S61 OR
S62 OR S63 OR S64 OR
S65 OR S66 OR S67 OR
S68 OR S69 OR S70 OR
S71 OR S72 OR S73 OR
S74 OR S75 OR S76 OR
S77 OR S78 OR S79 OR
S80 OR S81 OR S82 OR
S83 OR S84 OR S85 OR
S86 OR S87 OR S88 OR
S89 OR S90 OR S91 OR
S92 OR S93 OR S94 OR
S95 OR S96 OR S97 OR
S98 OR S99 OR S100
OR S101 OR S102 OR
S103 OR S104 OR S105
OR S106 OR S107 OR
S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114

S114 vafidemstat
S113 secukinumab or cosentyx
S112 ustekinumab or stelara
S111 (MH "Stem Cells+")
S110 upadacitinib or rinvoq
S109 selinexor
S108 "anti tumor necrosis factor agent*" or "anti tumour necrosis factor agent*" or "TNF inhibitor*" or "tumor necrosis factor inhibitor*"or "tumour necrosis factor inhibitor*"
S107 "tumor necrosis factor alpha inhibitor*" or "tumour necrosis factor alpha inhibitor*" or "antiTNF Agent*" or "anti tnf alpha agent*"
S106 tranilast or rizaben
S105 siltuximab
S104 sulphasalazine or salazopyrine or sulfasalazine or salazosulfapyridine
S103 tocilizumab or roactemra
S102 (MH "Tocilizumab")
S101 zilucoplan
S100 vMIP
S99 "stem cell*"
S98 (MH "Azathioprine")
S97 sarilumab or kevzara
S96 ruxolitinib or jakafi or jakavi
S95 rituximab or mabthera ortruxima
S94 (MH "Rituximab")
S93 (recombinant N2 "interleukin 7")
S92 (recombinant N2 "interleukin 2") or lymphocult

S91 ravulizumab or ultomiris
S90 prednisone
S89 (MH "Prednisone")
S88 prednisolone
S87 (MH "Prednisolone")
S86 pembrolizumab or keytruda or lambrolizumab
S85 PD-1 or gilvetmab or "programmed cell death 1 receptor"
S84 (MH "Programmed Cell Death Protein 1 Receptor")
S83 otilimab
S82 ocrelizumab or ocrevus
S81 ((nonsteroid* or “non steroid*”) adj (antiinflammatory or “anti inflammatory”) adj (drug* or agent*)) or NSAID*)
S80 (MH "Antiinflammatory Agents, Non-Steroidal")
S79 nintedanib or intedanib
S78 mycophenolate or "mycophenolic acid" or "mycophenolate mofetil" or myfortic
S77 (MH "Mycophenolic Acid") OR (MH "Mycophenolate Mofetil")
S76 methylprednisolone
S75 (MH "Methylprednisolone")
S74 methotrexate or metoject or nordimet or novatrex
S73 (MH "Methotrexate")
S72 mavrilimumab
S71 (MH "Mast Cells")
S70 "mast cell*" or mastocyte*
S69 mastinib
S68 leflunomide or arava
S67 (MH "Leflunomide")
S66 jakotinib
S65 ixekizumab or taltz
S64 IVIG
S63 (MH "Immunoglobulins intravenous")
S62 itolizumab
S61 Interferon*
S60 (MH "Interferons")
S59 "infliximab or flixabi or inflectra or remicade or remsima or renflexis
S58 (MH "Infliximab”)
S57 IMU-838
S56 immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or BRM therap*" or "immune therap*" or "immunoglobulin therap*"or "immunological therap*" or "immunological treatment*" or "immunological intervention*"
S55 (MH "Immunotherapy")
S54 immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*
S53 (MH "Immunoglobulins")
S52 imatinib or gleevac or gleevec or glivec
S51 (MH "Imatinib")
S50 IFX-1
S49 hydroxychloroquine or plaquenil
S48 (MH"Hydroxychloroquine")
S47 HCR040
S46 glucocorticoid*
S45 (MH "Glucocorticoids+")

S44 guselkumab or tremfya
S43 golimumab or simponi
S42 (MH "Golimumab")
S41 fingolimod or gilenia or
gilenya
S40 filgotinib
S39 fedratinib
S38 etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor fc fusion protein" or "tumour necrosis factor receptor fc fusion protein"
S37 (MH "Etanercept")
S36 eculizumab
S35 ebastine
S34 DFV890
S33 dexamethasone
S32 (MH "Dexamethasone")
S31 CYT-107
S30 cyclosporin
S29 (MH "Cyclosporine")
S28 corticosteroid* or"adrenal cortex hormone*" or "cortical steroid*" or "corticosteroid*" or corticoid* or "corticosteroid agent*"
S27 (MH "Adrenal Cortex Hormones+")
S26 colchicine
S25 (MH "Colchicine")
S24 CMAB806
S23 CIGB-258
S22 chloroquin*
S21 (MH "Chloroquine+")
S20 certolizumab
S19 (MH “Cell Therapy”)
S18 "cell based therap*" or "cell therap*" or "cellular therapy**
S17 canakinumab or ilaris
S16 brensocatib
S15 bevacizumab or avastin
S14 (MH "Bevacizumab")
S13 BDB-001
S12 baricitinib or olumiant
S11 azathioprine or arathioprin or arathioprine or immurel or imurel
S10 TD-0903
S9 advoralimab
S8 ARGX-117
S7 anakinra or kineret of "recombinant interleukin 1 receptor antagonist" or "recombinant interleukin 1 receptor blocker" or recombinant interleukin 1 receptor blocking agent"
S6 adalimumab or adaly or amgevita or amjevita or humira or imraldi or trudexaS5 (MH "Adalimumab")
S4 acalabrutinib or "acp196" or acp196 or calquence
S3 (ABX464
S2 (MH "Abatacept")
S1 abatacept or "CTLA4 Ig" or "CTLA4 immunoglobulin" or orencia

The Cochrane Library
Search Name: Covid & Therapy
Date Run: December 9, 2020
Comment: Cochrane - CENTRAL

ID	Search Hits
#1	MeSH descriptor: [Abatacept] explode all trees 273
#2	(Abatacept or "CTLA4 Ig" or "CTLA4 immunoglobulin" or orencia):ti,ab,kw 755
#3	(ABX464):ti,ab,kw 20
#4	(Acalabrutinib or "acp 196" or acp196 or calquence):ti,ab,kw 74
#5	MeSH descriptor: [Adalimumab] explode all trees 737
#6	(Adalimumab or adaly or amgevita or amjevita or humira or imraldi or trudexa):ti,ab,kw 2977
#7	MeSH descriptor: [Interleukin 1 Receptor Antagonist Protein] explode all trees 305
#8	(Anakinra or kineret or "recombinant interleukin 1 receptor antagonist" or "recombinant interleukin 1 receptor blocker" or "recombinant interleukin 1 receptor blocking agent"):ti,ab,kw 360
#9	(ARGX-117):ti,ab,kw0
#10	(avdoralimab):ti,ab,kw 1
#11	MeSH descriptor: [Azathioprine] explode all trees 1215
#12	(Azathioprine or arathioprin or arathioprine or immurel or imurel):ti,ab,kw 3186
#13	(Baricitinib or olumiant):ti,ab,kw 355
#14	(BDB-001):ti,ab,kw 1
#15	MeSH descriptor: [Bevacizumab] explode all trees 1896
#16	(Bevacizumab or avastin):ti,ab,kw 6112
#17	(Brensocatib):ti,ab,kw 0
#18	(Canakinumab or ilaris):ti,ab,kw 280
#19	MeSH descriptor: [Cell- and Tissue-Based Therapy] explode all trees 6100
#20	("cell based therapy" or "cell based therapies" or "cell therapy" or "cell therapies" or "cellular therapy" or "cellular therapies"):ti,ab,kw 1713
#21	(Certolizumab):ti,ab,kw 650
#22	MeSH descriptor: [Chloroquine] explode all trees 1160
#23	(Chloroquin*):ti,ab,kw 1503
#24	(CIGB-258):ti,ab,kw 0
#25	(CMAB806):ti,ab,kw 0
#26	MeSH descriptor: [Colchicine] explode all trees 335
#27	(Colchicine):ti,ab,kw 826
#28	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14272
#29	(corticosteroid* or "adrenal cortex hormone*" or "cortical steroid*" or "cortico steroid*" or corticoid* or "corticosteroid agent*"):ti,ab,kw 21772
#30	MeSH descriptor: [Cyclosporins] explode all trees 3157
#31	(Cyclosporin*):ti,ab,kw 7107
#32	(CYT-107):ti,ab,kw 4
#33	MeSH descriptor: [Dexamethasone] explode all trees 4489
#34	(Dexamethasone):ti,ab,kw 11427
#35	(DFV890):ti,ab,kw 1
#36	(Ebastine):ti,ab,kw 142
#37	(Eculizumab):ti,ab,kw 221
#38	MeSH descriptor: [Etanercept] explode all trees 754
#39	(Etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor Fc fusion protein" or "tumour necrosis factor receptor Fc fusion protein"):ti,ab,kw 2197
#40	(Fedratinib):ti,ab,kw 15

#41 (Filgotinib):ti,ab,kw 132
#42 MeSH descriptor: [Fingolimod Hydrochloride] explode all trees 146
#43 (Fingolimod or gilenia or gilenya):ti,ab,kw 548
#44 (Golimumab or simponi):ti,ab,kw 662
#45 (Guselkumab or tremfya):ti,ab,kw 186
#46 MeSH descriptor: [Glucocorticoids] explode all trees 4492
#47 (glucocorticoid*):ti,ab,kw 8445
#48 (HCR040):ti,ab,kw 1
#49 MeSH descriptor: [Hydroxychloroquine] explode all trees 463
#50 (Hydroxychloroquine or plaquenil):ti,ab,kw 1168
#51 (IFX-1):ti,ab,kw 17
#52 MeSH descriptor: [Imatinib Mesylate] explode all trees 399
#53 (Imatinib or gleevac or gleevec or glivec):ti,ab,kw 1396
#54 MeSH descriptor: [Immunoglobulins] explode all trees 25489
#55 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*):ti,ab,kw 13773
#56 MeSH descriptor: [Immunotherapy] explode all trees 7883
#57 (Immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or "BRM therap*" or "immune therap*" or "immunoglobulin therap*" or "immunological therap*" or "immunological treatment*" or "immunomodulatory intervention*"):ti,ab,kw 9839
#58 (IMU-838):ti,ab,kw 4
#59 MeSH descriptor: [Infliximab] explode all trees 720
#60 (Infliximab or flixabi or inflectra or remicade or remsima or renflexis):ti,ab,kw 2290
#61 MeSH descriptor: [Interferons] explode all trees 5775
#62 (Interferon*):ti,ab,kw 15371
#63 (Itolizumab):ti,ab,kw 18
#64 MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees 837
#65 (IVIG):ti,ab,kw 1322
#66 (Ixekizumab or taltz):ti,ab,kw 407
#67 (Jakotinib):ti,ab,kw 0
#68 MeSH descriptor: [Leflunomide] explode all trees 149
#69 (Leflunomide or arava):ti,ab,kw 625
#70 (Masitinib):ti,ab,kw 88
#71 MeSH descriptor: [Mast Cells] explode all trees 207
#72 ("mast cell*" or mastocyte*):ti,ab,kw 809
#73 (Mavrilimumab):ti,ab,kw 43
#74 MeSH descriptor: [Methotrexate] explode all trees 4127
#75 (Methotrexate or metoject or nordimet or novatrex):ti,ab,kw 11173
#76 (Methylprednisolone):ti,ab,kw 5203
#77 MeSH descriptor: [Methylprednisolone] explode all trees 2708
#78 MeSH descriptor: [Mycophenolic Acid] explode all trees 1356
#79 (Mycophenolate or (mycophenolic near acid) or myfortic or (mycophenolate near mofetil)):ti,ab,kw 4180
#80 (Nintedanib or intedanib):ti,ab,kw 465
#81 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees 7595
#82 ((NSAID* or "non steroid anti inflammatory agent*" or "non steroid anti inflammatory drug*" or "non steroidal anti inflammatory agent*" or "non steroidal anti inflammatory drug*" or "nonsteroid antiinflammatory agent*" or "nonsteroid antiinflammatory drug*" or "nonsteroidal antiinflammatory agent*" or "nonsteroidal antiinflammatory drug*" or "non steroid

antiinflammatory agent*" or "non steroid antiinflammatory drug*" or "non steroidal antiinflammatory agent*" or "non steroidal antiinflammatory drug*" or "nonsteroid anti inflammatory agent*" or "nonsteroid anti inflammatory drug*" or "nonsteroidal anti inflammatory agent*" or "nonsteroidal anti inflammatory drug*")):ti,ab,kw 8525
#83 (Ocrelizumab or ocrevus):ti,ab,kw 196
#84 (Otilimab):ti,ab,kw 6
#85 MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees 56
#86 (PD-1 or Gilvetmab or "programmed cell death 1 receptor"):ti,ab,kw 1714
#87 (Pembrolizumab or keytruda or lambrolizumab):ti,ab,kw 1417
#88 MeSH descriptor: [Prednisolone] explode all trees 4851
#89 (Prednisolone):ti,ab,kw 6988
#90 MeSH descriptor: [Prednisone] explode all trees 3951
#91 (Prednisone):ti,ab,kw 9425
#92 (Ravulizumab or ultomiris):ti,ab,kw 24
#93 ((recombinant near/2 "interleukin 2") or lymphocult):ti,ab,kw 195
#94 (recombinant near/2 "interleukin 7"):ti,ab,kw 17
#95 (recombinant near/2"interleukin 7"):ti,ab,kw 17
#96 MeSH descriptor: [Rituximab] explode all trees 1243
#97 (Rituximab or mabthera or truxima):ti,ab,kw 4625
#98 (Ruxolitinib or jakafi or jakavi):ti,ab,kw 378
#99 (Sarilumab or kevzara):ti,ab,kw 215
#100 (Secukinumab or cosentyx):ti,ab,kw 786
#101 (Selinexor):ti,ab,kw 69
#102 (Siltuximab):ti,ab,kw 59
#103 MeSH descriptor: [Stem Cells] explode all trees 775
#104 ("Stem cell*"):ti,ab,kw 10459
#105 MeSH descriptor: [Sulfasalazine] explode all trees 476
#106 (Sulphasalazine or salazopyrine or sulfasalazine or salazosulfapyridine):ti,ab,kw 1400
#107 (TD-0903):ti,ab,kw 2
#108 (Tocilizumab or roactemra):ti,ab,kw 1047
#109 (Tranilast or rizaben):ti,ab,kw 78
#110 ("tumor necrosis factor alpha inhibitor*" or "anti TNF agent*" or "anti TNF alpha agent*" or "anti tumor necrosis factor agent*" or "anti tumour necrosis factor agent*" or "TNF alpha inhibitor*" or "TNF inhibitor*" or "tumor necrosis factor inhibitor*" or "tumour necrosis factor alpha inhibitor*" or "tumour necrosis factor inhibitor*"):ti,ab,kw 864
#111 (Upadacitinib or rinvoq):ti,ab,kw 196
#112 (Ustekinumab or stelara):ti,ab,kw 759
#113 (Vafidemstat):ti,ab,kw 0
#114 (vMIP):ti,ab,kw 1
#115 (zilucoplan):ti,ab,kw 10
#116 {or #1-#115} 162188
#117 MeSH descriptor: [Coronavirus] explode all trees 35
#118 MeSH descriptor: [Coronavirus Infections] explode all trees 297
#119 (((corona* or corono*) near/1 (virus* or viral* or virinae*))):ti,ab,kw 52
#120 ((coronavirus* or coronovirus* or coronavirinae* or CoV)):ti,ab,kw 727
#121 (("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS

coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid)):ti,ab,kw 1106
#122 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes") 373
#123 {or #117-#122} 1345
#124 #116 and #123 444
#125 #124 with Publication Year from 2019 to present, in Trials 401

Online Supplementary Text S3: Search strategy for COVID-19 and rheumatic and musculoskeletal diseases.

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to November 2, 2020>
Search Strategy: Covid & RMD

---

1 exp Musculoskeletal Diseases/ (147749)
2 (musculoskeletal adj2 (disease* or disorder*)).mp. (6163)
3 exp Osteoarthritis/ (14140)
4 (degenerative adj2 arthritis).mp. dentifier, synonyms] (276)
5 osteoarthritis.mp. dentifier, synonyms] (29910)
6 exp Connective Tissue Diseases/ (38287)
7 (connective adj tissue adj2 (disease* or disorder*)).mp. dentifier, synonyms] (4407)
8 Rheumatic Diseases/ (1920)
9 (rheumatic adj2 (disease* or disorder*)).mp. dentifier, synonyms] (6738)
10 exp Lupus Erythematosus, Systemic/ (7514)
11 lupus.mp. dentifier, synonyms] (18771)
12 exp Antiphospholipid Syndrome/ (1225)
13 antiphospholipid.mp. dentifier, synonyms] (3162)
14 Sjogren's Syndrome/ (1816)
15 (sjogren* or sjoegren*).mp. dentifier, synonyms] (4095)
16 exp Scleroderma, Systemic/ (2839)
17 "systemic sclerosis".mp. dentifier, synonyms] (4615)
18 scleroderma.mp. dentifier, synonyms] (4808)
19 Scleroderma, Localized/ (461)
20 exp Arthritis, Rheumatoid/ (14699)
21 (rheumatoid adj2 arthritis).mp. dentifier, synonyms] (28128)
22 Arthritis, Psoriatic/ (1779)
23 (psoriatic adj2 arthritis).mp. dentifier, synonyms] (3993)
24 (psoriatic adj2 arthropathy).mp. dentifier, synonyms] (35)
25 Spondylitis, Ankylosing/ (2096)
26 (ankylosing adj2 spondylitis).mp. dentifier, synonyms] (4581)
27 (scleroderma adj2 (localised or localized)).mp. dentifier, synonyms] (606)
28 morphea.mp. dentifier, synonyms] (448)
29 Arthritis, Juvenile/ (1503)
30 (juvenile adj2 arthritis).mp. dentifier, synonyms] (2949)
31 exp Polymyositis/ (1237)
32 polymyositis.mp. dentifier, synonyms] (1163)
33 Dermatomyositis/ (1104)
34 dermatomyositis.mp. dentifier, synonyms] (2528)
35 dermatomyositides.mp. dentifier, synonyms] (0)
36 exp Spondylarthritis/ (4930)

37 (Spondyloarthritis or spondylarthritis or spondarthritis or (spinal adj2 arthritis)).mp. dentifier, synonyms] (2736)
38 Fibromyalgia/ (1486)
39 fibromyalgia.mp. dentifier, synonyms] (3589)
40 Gout/ (1564)
41 gout.mp. dentifier, synonyms] (4338)
42 exp Chondrocalcinosis/ (263)
43 chondrocalcinosis.mp. dentifier, synonyms] (325)
44 (calcium adj pyrophosphate adj2 disease*).mp. dentifier, synonyms] (107)
45 (calcium adj pyrophosphate adj2 deposition).mp. dentifier, synonyms] (184)
46 pseudogout.mp. dentifier, synonyms] (158)
47 exp Vasculitis/ (9001)
48 vasculitis.mp. dentifier, synonyms] (10442)
49 Angiitis.mp. dentifier, synonyms] (342)
50 Angiitides.mp. dentifier, synonyms] (0)
51 angitis.mp. dentifier, synonyms] (18)
52 (vascular adj2 inflammation).mp. dentifier, synonyms] (2473)
53 (vasculitic adj2 lesion*).mp. dentifier, synonyms] (43)
54 Angioitis.mp. dentifier, synonyms] (0)
55 exp Sarcoidosis/ (2191)
56 Sarcoid.mp. dentifier, synonyms] (739)
57 Sarcoidosis.mp. dentifier, synonyms] (5162)
58 ("Besnier Boeck" adj2 (disease or syndrome)).mp. dentifier, synonyms] (1)
59 ("Besnier Boeck Schaumann" adj2 (disease or syndrome)).mp. dentifier, synonyms] (1)
60 Sarcoidoses.mp. dentifier, synonyms] (1)
61 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (238373)
62 exp Coronavirus/ (19595)
63 exp Coronavirus Infections/ (20991)
64 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (38713)
65 "severe acute respiratory syndrome*".ti,ab,kw,kf. (6855)
66 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1388)
67 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (28750)
68 62 or 63 or 64 or 65 or 66 or 67 (51103)
69 61 and 68 (685)
70 limit 69 to yr="2019 -Current" (615)

Embase
Database: Embase <1996 to November 2, 2020>
Search Strategy: Covid & RMD
---

1 exp musculoskeletal disease/ (1805492)
2 (musculoskeletal adj2 (disease* or disorder*)).mp. (39744)
3 exp osteoarthritis/ (112778)
4 osteoarthritis.mp. (125888)
5 (degenerative adj2 arthritis).mp. (1182)
6 exp connective tissue disease/ (342785)
7 (connective adj tissue adj2 (disease* or disorder*)).mp. (25810)
8 exp rheumatic disease/ (191065)
9 (rheumatic adj2 (disease* or disorder*)).mp. (51642)
10 exp systemic lupus erythematosus/ (71140)
11 lupus.mp. (107596)
12 antiphospholipid syndrome/ (15875)
13 antiphospholipid.mp. (21828)
14 Sjoegren syndrome/ (17933)
15 (sjogren* or sjoegren*).mp. (24026)
16 exp systemic sclerosis/ (25333)
17 "systemic sclerosis".mp. (26622)
18 scleroderma.mp. (20606)
19 exp localized scleroderma/ (2942)
20 exp rheumatoid arthritis/ (158914)
21 (rheumatoid adj2 arthritis).mp. (173099)
22 psoriatic arthritis/ (21021)
23 (psoriatic adj2 arthritis).mp. (22500)
24 (psoriatic adj2 arthropathy).mp. (278)
25 ankylosing spondylitis/ (21379)
26 (ankylosing adj2 spondylitis).mp. (25741)
27 (scleroderma adj2 (localised or localized)).mp. (1585)
28 morphea/ (1922)
29 morphea.mp. (2328)
30 exp juvenile rheumatoid arthritis/ (17280)
31 (juvenile adj2 arthritis).mp. (18619)
32 polymyositis/ (6533)
33 polymyositis.mp. (8219)
34 exp dermatomyositis/ (12670)
35 dermatomyositis.mp. (13758)
36 dermatomyositides.mp. (1)
37 spondylarthritis/ (7587)
38 spondylarthritis.mp. (7862)
39 fibromyalgia/ (19185)
40 fibromyalgia.mp. (20622)
41 gout/ (16602)
42 gout.mp. (18924)
43 chondrocalcinosis/ (1061)
44 chondrocalcinosis.mp. (1276)
45 (calcium adj pyrophosphate adj2 disease*).mp. (296)
46 (calcium adj pyrophosphate adj2 deposition).mp. (565)
47 pseudogout.mp. (1055)
48 exp vasculitis/ (86672)
49 vasculitis.mp. (63781)
50 Angiitis.mp. (1563)
51 Angiitides.mp. (4)

52 angitis.mp. (184)
53 (vascular adj2 inflammation).mp. (9818)
54 (vasculitic adj2 lesion*).mp. (341)
55 Angioitis.mp. (1)
56 exp sarcoidosis/ (26462)
57 Sarcoid.mp. (3644)
58 Sarcoidosis.mp. (31208)
59 ("Besnier Boeck" adj2 (disease or syndrome)).mp. (3)
60 ("Besnier Boeck Schaumann" adj2 (disease or syndrome)).mp. (4)
61 Sarcoidoses.mp. (21)
62 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (2075430)
63 exp Coronavirinae/ (16754)
64 exp Coronavirus infection/ (17958)
65 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (35694)
66 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (1168)
67 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (37658)
68 "severe acute respiratory syndrome*".ti,ab,kw. (9296)
69 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (33830)
70 63 or 64 or 65 or 66 or 67 or 68 or 69 (64189)
71 62 and 70 (2467)
72 limit 71 to yr="2019 -Current" (1776)

CINAHL to be added
November 2, 2020

S71 S61 AND S69
S70 S61 AND S69
S69 S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68
S68 (MH "Coronavirus+")
S67 "severe acute respiratory syndrome*"
S66 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV- 2019*" or nCoV19* or"nCoV-19*" or "COVID-19*" or COVID19* or"COVID-2019*" orCOVID2019* or "HCoV-19*" or HCoV19* or"HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARSCoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid)

S65 (coronavirus* or coronovirus* or coronavirinae* or CoV)
S64 ((corona* or corono*) N1 (virus* or viral* or virinae*)).
S63 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").S116 (MH "Coronavirus Infections+")
S62 (MH "Coronavirus Infections+")
S61 S1 OR S2 OR S3 OR S4
OR S5 OR S6 OR S7 OR
S8 OR S9 OR S10 OR
S11 OR S12 OR S13 OR
S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR
S20 OR S21 OR S22 OR
S23 OR S24 OR S25 OR
S26 OR S27 OR S28 OR
S29 OR S30 OR S31 OR
S32 OR S33 OR S34 OR
S35 OR S36 OR S37 OR
S38 OR S39 OR S40 OR
S41 OR S42 OR S43 OR
S44 OR S45 OR S46 OR
S47 OR S48 OR S49 OR
S50 OR S51 OR S52 OR
S53 OR S54 OR S55 OR
S56 OR S57 OR S58 OR
S59 OR S60
S60 (MH "Spondylarthritis+")
S59 scleroderma
S58 (MH "Scleroderma, Systemic+")
S57 sjogren* or sjoegren*
S56 (MH "Sjogren's Syndrome")
S55 sarcoidoses
S54 sarcoidosis
S53 "besnier boeck schaumann" N2 (disease or syndrome)
S52 "besnier boeck" N2 (disease or syndrome)
S51 (MH "Sarcoidosis")
S50 sarcoid
S49 angioitis
S48 vasculitic N2 lesion*
S47 vascular N2 inflammation
S46 angitis
S45 antiphospholipid
S44 angiitides
S43 angiitis
S42 vasculitis
S41 (MH "Vasculitis+")
S40 pseudogout
S39 "calcium pyrophosphate" N2 deposition
S38 "calcium pyrophosphate" N2 disease*
S37 chondrocalcinosis
S36 (MH "Chondrocalcinosis")
S35 gout
S34 (MH "Antiphospholipid Syndrome")

S33 (MH "Gout")
S32 fibromyalgia
S31 (MH "Fibromyalgia")
S30 Spondyloarthritis or spondylarthritis or spondarthritis or (spinal adj2 arthritis)
S29 dermatomyositides
S28 dermatomyositis
S27 (MH "Dermatomyositis")
S26 polymyositis
S25 (MH "Polymyositis+")
S24 juvenile N2 arthritis
S23 lupus
S22 (MH "Arthritis, Juvenile Rheumatoid")
S21 "morphea"
S20 scleroderma N2 (localised or localized)
S19 ankylosing N2 spondylitis
S18 (MH "Spondylitis, Ankylosing")
S17 psoriatic N2 arthropathy
S16 psoriatic N2 arthritis
S15 (MH "Arthritis, Psoriatic")
S14 rheumatoid N2 arthritis
S13 (MH "Arthritis, Rheumatoid+")
S12 (MH "Lupus Erythematosus, Systemic+")
S11 (MH "Scleroderma, Circumscribed")
S10 "systemic sclerosis"
S9 rheumatic N2 (disease* or disorder*)
S8 (MH "Rheumatic Diseases+")
S7 "connective tissue" N2 (disease* or disorder*)
S6 (MH "Connective Tissue Diseases+")
S5 degenerative N2 arthritis
S4 osteoarthritis
S3 (MH "Osteoarthritis+")
S2 (musculoskeletal N2 (disease* or disorder*)
S1 (MH "Musculoskeletal Diseases+")

The Cochrane Library
November 2, 2020

ID	Search Hits
#1	MeSH descriptor: [Musculoskeletal Diseases] explode all trees 40204
#2	(musculoskeletal near/2 (disease* or disorder*)):ti,ab,kw 4971
#3	MeSH descriptor: [Osteoarthritis] explode all trees 7366
#4	(Osteoarthritis):ti,ab,kw 17270
#5	(degenerative near/2 arthritis):ti,ab,kw 78
#6	MeSH descriptor: [Connective Tissue Diseases] explode all trees 9484
#7	("connective tissue" near/2 disease*):ti,ab,kw 1697
#8	("connective tissue" near/2 disorder*):ti,ab,kw 608
#9	MeSH descriptor: [Rheumatic Diseases] explode all trees 15387
#10	(rheumatic near/2 (disease* or disorder*)):ti,ab,kw 2842
#11	MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees 1025

#12 (lupus):ti,ab,kw 3035
#13 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees 90
#14 (antiphospholipid):ti,ab,kw 452
#15 MeSH descriptor: [Sjogren's Syndrome] explode all trees 283
#16 (sjogren* or Sjoegren*):ti,ab,kw 764
#17 MeSH descriptor: [Scleroderma, Systemic] explode all trees 541
#18 ("systemic sclerosis"):ti,ab,kw 1099
#19 (scleroderma):ti,ab,kw 1117
#20 MeSH descriptor: [Scleroderma, Localized] explode all trees 82
#21 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 6056
#22 (rheumatoid near/2 arthritis):ti,ab,kw 15306
#23 MeSH descriptor: [Arthritis, Psoriatic] explode all trees 431
#24 (psoriatic near/2 arthritis):ti,ab,kw 1946
#25 psoriatic near/2 arthropathy 29
#26 MeSH descriptor: [Spondylitis, Ankylosing] explode all trees 677
#27 (ankylosing near/2 spondylitis):ti,ab,kw 1982
#28 (scleroderma near/2 (localised or localized)):ti,ab,kw 108
#29 (morphea):ti,ab,kw 35
#30 MeSH descriptor: [Arthritis, Juvenile] explode all trees 294
#31 (juvenile near/2 arthritis):ti,ab,kw 849
#32 MeSH descriptor: [Polymyositis] explode all trees 93
#33 (polymyositis):ti,ab,kw 177
#34 MeSH descriptor: [Dermatomyositis] explode all trees 87
#35 (dermatomyositis):ti,ab,kw 295
#36 (dermatomyositides):ti,ab,kw 0
#37 MeSH descriptor: [Spondylarthritis] explode all trees 1289
#38 (Spondyloarthritis or spondylarthritis or spondarthritis or (spinal near/2 arthritis)):ti,ab,kw 893
#39 MeSH descriptor: [Fibromyalgia] explode all trees 1363
#40 (fibromyalgia):ti,ab,kw 2935
#41 MeSH descriptor: [Gout] explode all trees 360
#42 (gout):ti,ab,kw 1391
#43 MeSH descriptor: [Chondrocalcinosis] explode all trees 15
#44 (chondrocalcinosis):ti,ab,kw 19
#45 ("calcium pyrophosphate" near/2 disease*):ti,ab,kw 8
#46 ("calcium pyrophosphate" near/2 deposition):ti,ab,kw 10
#47 (pseudogout):ti,ab,kw 13
#48 MeSH descriptor: [Vasculitis] explode all trees 1978
#49 (vasculitis):ti,ab,kw 1240
#50 (Angiitis):ti,ab,kw 19
#51 (Angiitides):ti,ab,kw 0
#52 (angitis):ti,ab,kw 2
#53 (vascular near/2 inflammation):ti,ab,kw 609
#54 (vasculitic near/2 lesion*):ti,ab,kw 3
#55 (Angioitis):ti,ab,kw 0
#56 (Sarcoid):ti,ab,kw 40
#57 (Sarcoidosis):ti,ab,kw 611
#58 MeSH descriptor: [Sarcoidosis] explode all trees 214
#59 ("Besnier Boeck" near/2 (disease or syndrome)):ti,ab,kw 0
#60 ("Besnier Boeck Schaumann" near/2 (disease or syndrome)):ti,ab,kw 0
#61 (Sarcoidoses):ti,ab,kw 0

#62 {or #1-#61} 76539
#63 MeSH descriptor: [Coronavirus] explode all trees 35
#64 MeSH descriptor: [Coronavirus Infections] explode all trees 297
#65 (((corona* or corono*) near/1 (virus* or viral* or virinae*))):ti,ab,kw 52
#66 ((coronavirus* or coronovirus* or coronavirinae* or CoV)):ti,ab,kw 727
#67 (("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid)):ti,ab,kw 1106
#68 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes") 373
#69 {or #63-#68} 1345
#70 #62 and #69 38
#71 #70 with Publication Year from 2019 to present, in Trials 32

Online supplemental Text S4: Research questions and PICOs

Research Questions-Pathogenesis (I)

1	Is pathophysiology of COVID-19 at some phase immune mediated?
2	What pro-inflammatory cytokines and chemokines are predominant at different stages of COVID infection? Which are primary and which are downstream?
5	What is the role of type 1, type 2 and type 3 interferon and IFN-inducible genes?
6	What are the lymphocyte subset abnormalities at different stages of COVID-19 infection?
12	What is the role of mast cell abnormalities at different stages of COVID-19 infection?
13	What is the role of neutrophils at different stages of COVID-19 infection?
14	Is there any relationship between viral replication/load and the immune response?
15	Is the immunoprotection against COVID-19 antibody dependent or cellular dependent?
16	Is there a role of antibody dependent enhancement and detrimental effect of anti-SARS-CoV2 antibodies (e.g. by stimulation of macrophages)?
17	What is the time to anti-COVID-19 immunoglobulin generation and relation (if any) with clinical outcomes?
20	Does SARS-CoV2 exert a superantigen effect?
21	Does immunosenescence play a role in the response to SARS-CoV2?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention SOC Any immunomodulatory intervention (*see Appendix 1 for compounds*)
C	Comparator	No comparator Baseline SOC Same immunomodulatory agent at different dose/interval/way of administration Other immunomodulatory agent
O	Outcome	Total and partial WBC count, WBC % (L, N, Mo, N), CD4/CD8 ratio, % of CD3+ T cells, Th1, Th2, Th17, Treg, Thf, % of CD19 cells, % Breg, % of CD16+ cells, % Mo subsets, % N subsets, N/L ratio, % mast cells, platelet count, SARS-CoV2 specific T cells, B cells and Ig, concentration of cytokines, concentration of chemokines
S	Sample	Any biologic sample (*see Appendix 2*)

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any technique assessing phenotype and function of immune and non-immune cells Any analysis of the concentration of soluble mediators Any technique assessing SARS-CoV2 structure and physiopathological mechanisms
C	Comparator	No comparator Baseline Any stage of the disease evolution Before/After any treatment-immunomodulatory agent
O	Outcome	Monocytes/Macrophages activation, function and polarization; T cells (Th1, Th2, Th17, Treg, Thf, NK, GammaDelta T cells) activation, function and differentiation; B cells and plasmocytes activation, function, differentiation and Ig production, PNN, Mast cells, dendritic cells activation and function, endothelial cells activation and function, fibroblasts activation and function, Interferon production, cytokines/chemokines production, underlying molecular pathways (NFkB, JAK/STAT…), complement activation, SARS-CoV2 structure, replication and mechanisms of action, SARS-CoV2 interactions with any cell type, senescent cells, T cell exhaustion.
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Any biologic sample

Research questions-pathogenesis (II)

3	Is it possible to clearly demarcate distinct stages of the disease, with specific biomarkers for each stage?
22	Are there immune profiles/signatures associated with disease severity or phenotypes?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention SOC Any immunomodulatory intervention (*see Appendix 1 for compounds*)
C	Comparator	No comparator Baseline SOC Same immunomodulatory agent at different dose/interval/way of administration Other immunomodulatory agent
O	Outcome	Total and partial WBC count, WBC % (L, N, Mo, N), CD4/CD8 ratio, % of CD3+ T cells, Th1, Th2, Th17, Treg, Thf, % of CD19 cells, % Breg, % of

		CD16+ cells, % Mo subsets, % N subsets, N/L ratio, % mast cells, SARS-CoV2 specific T cells, B cells and Ig, concentration of cytokines, concentration of chemokines, concentration of: ferritin, D dimer, LDH, SAA, CRP, ESR, platelet count, creatinine, urea, cardiac troponin. Any other measurement related to clinical and radiological outcomes
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Any biologic sample

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any analysis of the concentration of soluble mediators
C	Comparator	No comparator Baseline Any stage of the disease evolution Before/After any treatment-immunomodulatiory agent
O	Outcome	Immunotypes, cellular signatures, molecular signatures, Interferon production, cytokines/chemokines production, complement activation, underlying molecular pathways (NFkB, JAK/STAT…), by any cell type *(See Appendix 3)*
S	Sample	Any biologic sample (*see Appendix 2*)

Research questions-pathogenesis (III)

4	Are there endotypic variants that predispose to more severe COVID-19 outcomes?
10	Which genetically determined differences in individual immune response and concomitant diseases may contribute to the development of cytokine release syndrome?
18	Do blood groups (Rhesus and AB0) or HLA genes play any role in the susceptibility to develop severe COVID-19?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention Any intervention
C	Comparator	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection AND with different HLA haplotypes/blood groups/other known genotypes
O	Outcome	Total and partial WBC count, WBC % (L, N, Mo, N), CD4/CD8 ratio, % of CD3+ T cells, Th1, Th2, Th17, Treg, Thf, % of CD19 cells, % Breg, % of CD16+ cells, % Mo subsets, % N subsets, N/L ratio, % mast cells, SARS-CoV2 specific T cells, B cells and Ig, concentration of cytokines, concentration of chemokines, concentration of: ferritin, D dimer, LDH, SAA, CRP, ESR, platelet count, creatinine, urea, cardiac troponin. Any other measurement related to clinical and radiological outcomes
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Any biologic sample (*see Appendix 2*)

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any study assessing gene expression of immune and non-immune cells
C	Comparator	No comparator Any other comparator (other disease, different populations…)
O	Outcome	GWAS Polymorphisms (SNPs) Bulk RNA sequencing Single cell RNA sequencing miRs arrays
S	Sample	Any biologic sample (*see Appendix 2*)

Research questions-pathogenesis (IV)

7	What is the mechanism of endothelial dysfunction and thrombosis?
8	What is the role of complement in endothelial dysfunction?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention SOC Any immunomodulatory intervention
C	Comparator	No comparator Baseline SOC Same immunomodulatory agent at different dose/interval/way of administration Other immunomodulatory agent
O	Outcome	D-dimer, fibrinogen, vWf, platelet count, markers of platelet activation (e.g. P-selectin), ICAM, VCAM, circulating endothelial cell count, anti-phospholipid antibodies, endothelial microparticles, complement fractions
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Any biologic sample (*see Appendix 2*)

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any study assessing endothelial dysfunction
C	Comparator	No comparator Baseline Any stage of the disease evolution

		Before/After any treatment-immunomodulatiory agent
O	Outcome	Endothelial cells activation and function, Complement activation, Platelets function and activation, platelets microparticles release, Interaction of Endothelial cells and platelets with any other cells *(see Appendix 3*) or with the SARS-CoV2 virus, adhesion molecules (ICAM, VCAM…) expression
S	Sample	Any biologic sample (*see Appendix 2*)

Research questions-pathogenesis (V)

9	Which is the spectrum of histological abnormalities in COVID-19 pneumonia and their correlations with the clinical picture?

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention SOC Any immunomodulatory intervention (*see Appendix 1 for compounds*)
C	Comparator	No comparator Baseline SOC Same immunomodulatory agent at different dose/interval/way of administration Other immunomodulatory agent
O	Outcome	Any histological finding (e.g. inflammatory infiltrate and its features, cytokine expression…)
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Bronchial endothelial cells from BAL Ante-mortem lung/airway biopsies Post-mortem lung/airway tissue

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any study assessing bronchial endothelial cells function
C	Comparator	No comparator Baseline Any stage of the disease evolution Before/After any treatment-immunomodulatiory agent
O	Outcome	Bronchial endothelial cells function, activation and chemokines/cytokines secretion, Bronchial endothelial cells interactions with any other cell type *(see Appendix 3)*
S	Sample	Bronchial endothelial cells from BAL

Research questions-pathogenesis (VI)

11	Which are the differences in COVID-19 pathogenesis in the adult and pediatric populations?

In vivo

P	Patients	Adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention Any intervention
C	Comparator	Pediatric patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
O	Outcome	Any clinical and laboratory variable as per other PICOs
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Any biologic sample (*see Appendix 2*)

In vitro

P	Patients	Adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any technique assessing phenotype and function of immune and non-immune cells Any study assessing endothelial dysfunction Any study assessing gene expression of immune and non-immune cells Any analysis of the concentration of soluble mediators
C	Comparator	Pediatric patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
O	Outcome	Any cell function, activation, interaction with SARS-Cov2 as per other PICOs
S	Sample	Any biologic sample (*see Appendix 2*)

Research questions-pathogenesis (VII)

19	Does the gut play any role (e.g. increased IgA permeability) in COVID-19 pathogenesis
22	Do comorbidities (e.g. obesity) affect the immune response against SARS-COV2?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention SOC Any immunomodulatory intervention (*see Appendix 1 for compounds*)
C	Comparator	No comparator Baseline SOC Same immunomodulatory agent at different dose/interval/way of administration Other immunomodulatory agent
O	Outcome	BMI, abdominal fat evaluation, bowel biopsy, endoscopic findings
T	Time	Cross sectional, longitudinal and retrospective studies
S	Sample	Any biologic sample (*see Appendix 2*)

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any technique assessing phenotype and function of immune and non-immune cells Any study assessing gut epithelia dysfunction
C	Comparator	Baseline Any stage of the disease evolution Before/After any treatment-immunomodulatiory agent Other intestinal diseases such as IBDs
O	Outcome	Gut epithelial cells function and activation, Gut epithelial cells interactions with other immune cells (T cells, B cells, DCs, macrophages, PNN, Mast cells) or SARS-CoV2, gut permeability to IGs, complement activation, effects of systemic inflammation caused by comorbidities on any cells described in *Appendix 3.*
S	Sample	Any biologic sample (*see Appendix 2*)

Research questions-Immunomodulatory treatment

1	What is the efficacy and safety of immune-modulatory drugs (hydroxychloroquine, glucocorticoids, tocilizumab, sarilumab, siltuximab, anakinra, colchicine, JAKi, mavrilimumab, anti GM-CSFR Mab, inhalatory IFN etc.) in COVID-19?
2	What are the consequences of immune-modulatory drugs on viral load and host anti-viral immune response?
3	What is the risk of secondary infections?
4	Is it possible to clearly demarcate distinct stages of the disease with stratified interventions for each stage?
5	Can Dexamethasone be considered as the standard of care after the RECOVERY study?
6	Can Dexamethasone be combined with other anti-cytokines and if so at which disease stage?
7	Should anti-cytokine agents be combined with dexamethasone or used as an alternative (e.g. steroid sparing)?
8	Is there a room for an association of anti-viral drugs or interferon and immunomodumators (Dexamethasone +/- anti-cytokines)?
9	Can any corticosteroid be used with the same efficacy in COVID-19 or is dexamethasone more effective than others?
10	Is combined immunotherapy more effective and safe than sequential immunotherapy?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without an RMDs prior SARS-CoV2 infection
I	Intervention	Any immunomodulatory intervention
C	Comparator	No comparator Baseline SOC Same immunomodulatory agent at different dose/interval/way of administration Same immunomodulatory agent in severe vs mild/moderate COVID-19 Other immunomodulatory agent (same or different mechanism of action)
O	Outcome	Efficacy outcomes: Admission to ICU, death, discharge, disease state (composite scores), recovery (no symptoms/signs and/or negative diagnostic test), viral load, imaging features of involved sites (e.g. lungs) Safety outcomes: AEs, SAEs (including among others QT elevation and secondary infections)
T	Time	Longitudinal observational, retrospective, RCTs
S	Sample	No biologic sample (for studies with only clinical/imaging outcomes) Any biologic sample for SARS-CoV2 detection before and after treatment

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND without a RMDs prior SARS-CoV2 infection (RMD treated with any compound)

I	Intervention	Any technique assessing phenotype and function of immune and non-immune cells Any study assessing gene expression of immune and non immune cells Any analysis of the concentration of soluble mediators
C	Comparator	No comparator Baseline Any stage of the disease evolution Before/During/After any treatment-immunomodulatory agent
O	Outcome	Effect of any immunomodulatory drug alone or in combination (*see Appendix 1*) on Monocytes/Macrophages activation, function and polarization; T cells (Th1, Th2, Th17, Treg, Thf, NK, GammaDelta T cells) activation, function and differentiation; B cells and plasmocytes activation, function, differentiation and Ig production, PNN, Mast cells, dendritic cells activation and function, endothelial cells activation and function, fibroblasts activation and function, Interferon production, cytokines/chemokines production, underlying molecular pathways (NFkB, JAK/STAT…), complement activation, SARS-CoV2 structure, replication and mechanisms of action, SARS-CoV2 interactions with any cell type
S	Sample	Any biologic sample

Research questions-COVID-19 and RMDs

	Is SARS-CoV2 a trigger for autoimmune diseases?

In vivo

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND **without** an RMDs prior SARS-CoV2 infection
I	Intervention	No intervention Any intervention
C	Comparator	No comparator Any comparator
O	Outcome	New onset autoimmune disease (fulfilling corresponding classification criteria) OR new onset of isolated symptoms/signs associated with laboratory abnormalities (e.g. ANA+ Raynaud's phenomenon)
T	Time	Longitudinal observational, RCTs and retrospective studies
S	Sample	Any biologic sample (*see Appendix 2*)

In vitro

P	Patients	Pediatric and adult patients with proven SARS-CoV2 infection AND with clinical features of COVID-19 OR with asymptomatic/paucisymptomatic infection AND **WITHOUT** RMDs prior SARS-CoV2 infection (RMD treated with any compound)
I	Intervention	Any technique assessing phenotype and function of immune and non-immune cells

		Any analysis of the concentration of soluble mediators
C	Comparator	No comparator Baseline Any stage of the disease evolution
O	Outcome	Monocytes/Macrophages activation, function and polarization; T cells (Th1, Th2, Th17, Treg, Thf, NK, GammaDelta T cells) activation, function and differentiation; B cells and plasmocytes activation, function, differentiation and Ig production, PNN, Mast cells, dendritic cells activation and function, endothelial cells activation and function, fibroblasts activation and function, Interferon production, cytokines/chemokines production, underlying molecular pathways (NFkB, JAK/STAT…), complement activation, SARS-CoV2 structure, replication and mechanisms of action, SARS-CoV2 interactions with any cell type *(See appendix 3).*GWAS, Polymorphisms (SNPs), Bulk RNA sequencing, Single cell RNA sequencing (Any cell, *see Appendix 3),* miRs arrays.
S	Sample	Any biologic sample (*see Appendix 2*)

Online Supplemental Text S5: Eligibility criteria for studies on COVID-19 and therapy

- Original research articles
- Published in peer-reviewed journals
- English language
- Adults
- Proven SARS-CoV2 infection according to the reference standard (nucleic acid amplification tests such as RT-qPCR)
- Signs/symptoms of COVID-19 or asymptomatic SARS-CoV2 infection
- Intervention: any immunomodulatory drug investigated or under investigation in SARS-CoV-2 infection according to the WHO International Clinical Trials Registry Platform as of 9 July 2020
- Any comparator or no comparator
- Any study design
- No diagnosis of RMDs prior SARS-CoV2 infection

On line supplementary Text S6: Risk of Bias evaluation tools.

Randomized Controlled Trials: Revised Cochrane risk-of-bias tool for randomized trials (RoB2)

Version of 22 August 2019

Study details

Reference

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Comparator:

Specify which outcome is being assessed for risk of bias

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Non-randomized studies of interventions: The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	
Experimental intervention	
Comparator	
Outcomes	

List the confounding domains relevant to all or most studies

List co-interventions that could be different between intervention groups and that could impact on outcomes

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants	
Experimental intervention	
Comparator	

Is your aim for this study…?

☐ to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?

			Yes / No / No information	Favour experimental / Favour comparator / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	Description	Response options
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		Y / PY / PN / N
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA / Y / PY / PN / N / NI

Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?		NA / Y / PY / PN / N / NI
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA / Y / PY / PN / N / NI
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to confounding?		Favours experimental / Favours comparator / Unpredictable

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4		Y / PY / PN / N / NI
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?		NA / Y / PY / PN / N / NI
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
2.4. Do start of follow-up and start of intervention coincide for most participants?		Y / PY / PN / N / NI
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of participants into the study?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?		Y / PY / PN / N / NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y / PY / PN / N / NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to classification of interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		Y / PY / PN / N / NI
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA / Y / PY / PN / N / NI
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		Y / PY / PN / N / NI
4.4. Was the intervention implemented successfully for most participants?		Y / PY / PN / N / NI
4.5. Did study participants adhere to the assigned intervention regimen?		Y / PY / PN / N / NI
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?		Y / PY / PN / N / NI
5.2 Were participants excluded due to missing data on intervention status?		Y / PY / PN / N / NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?		Y / PY / PN / N / NI
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?		NA / Y / PY / PN / N / NI
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to missing data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		Y / PY / PN / N / NI
6.2 Were outcome assessors aware of the intervention received by study participants?		Y / PY / PN / N / NI
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y / PY / PN / N / NI
6.4 Were any systematic errors in measurement of the outcome related to intervention received?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to measurement of outcomes?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1. ... multiple outcome *measurements* within the outcome domain?		Y / PY / PN / N / NI
7.2 ... multiple *analyses* of the intervention-outcome relationship?		Y / PY / PN / N / NI
7.3 ... different *subgroups*?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall bias		
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

On line supplementary Table S1: Flowchart of the 3 searches (Part 1)

	TOTAL	COVID-19 AND pathogenesis	COVID-19 AND therapy	COVID-19 AND RMDs
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	18465	10847	6746	872
Embase	34843	16321	15508	3014
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	4604	1643	2709	252
The Cochrane Central Register of Controlled Trials (CENTRAL)	2460	732	1680	48
TOTAL	60372	29543	26643	4186
DUPLICATES (within groups + between groups)	32458	11548	18337	2573
TITLES AND ABSTRACTS SCREENED	27914	17995	8306	1613
EXCLUDED:	26213	17144	7708	1361
Other topic (no COVID-19)	1562	1342	181	39
Other topic (COVID-19)	9330	6182	2621	527
Other therapies for COVID-19 (e.g. antivirals)	586	469	112	5
Narrative revies, commentaries, viewpoints, editorials	9205	6259	2378	568
Systematic literature reviews	647	350	255	42
Case reports unless on immunomodulatory treatments	1339	692	602	75
Study protocols	2373	1137	1181	55
Other language	238	121	95	22

Recommendations/guidelines/position papers	245	79	142	24
Conference abstracts	71	8	63	0
Erratum/Corrections/Retractions	112	70	41	1
Animal studies	119	104	15	0
Preprints	386	331	52	3

INCLUDED FOR FULL TEXT ASSESSMENT	1710	860	568	252
PATHOGENESIS	586	423	140	23
THERAPY	700	298	398	4
RMDs	394	139	30	225

On line supplementary Table S2: Flowchart of the 3 searches (Part 2)

	TOTAL	COVID-19 AND pathogenesis	COVID-19 AND therapy	COVID-19 AND RMDs	Handsearch
FULL TEXTS EVALUATED	707	298	398	4	7
EXCLUDED	**306**	151	151	4	0
Narrative reviews, commentaries, viewpoints, editorials	103	53	48	2	0
Systematic literature reviews	15	9	6	0	0
Wrong population	31	18	11	2	0
Study protocols	18	10	8	0	0
Conference abstracts	10	9	1	0	0
Other language	15	8	7	0	0
Other topic related to COVID	70	24	46	0	0
Wrong intervention	12	6	6	0	0
Duplicates	32	14	18	0	0
INCLUDED IN THE SLR	**401**	147	247	0	7
Tocilizumab	138	28	110	0	0
Corticosteroids	65	21	44	0	0
Hydroxychloroquine	53	13	40	0	0
Convalescent plasma	42	37	5	0	0
Anakinra	19	12	7	0	0
Mesenchymal stem cells	13	7	6	0	0
Intravenous immunoglobulins	12	5	7	0	0
Baricitinib	6	3	3	0	1
Tocilizumab + glucocorticoids	6	2	4	0	0
Ruxolitinib	7	3	4	0	1
Interferon beta 2a	6	4	2	0	0
Colchicine	4	4	0	0	0
Sarilumab	3	2	1	0	0
Eculizumab	3	0	1	0	2
Leflunomide	2	2	0	0	0
Baricitinib + glucocorticoids	3	0	1	0	0

Mavrilimumab	1	1	0	0	0
Vilobelimab	1	0	1	0	0
Ruxolitinib + eculizumab	1	1	0	0	0
rhIL-7	2	1	1	0	0
Interferon alpha 2b	1	0	1	0	0
Interferon kappa	1	0	1	0	0
Infliximab	1	1	0	0	0
Canakinumab	2	0	2	0	0
Imatinib	1	0	1	0	0
Ruxolitinib+glucocorticoids	1	0	1	0	0
Anakinra + glucocorticoids	1	0	1	0	0
Cyclosporin + glucocorticoids	1	0	1	0	0
Lenzilumab	1	0	1	0	0
Itolizumab	1	0	1	0	0
AMY-101	1	0	0	0	1
Tesidolumab	1	0	0	0	1
Treg cells	1	0	0	0	1

On line supplementary Table S3: Design of studies retrieved by the SLR.

Alunno A, *et al. Ann Rheum Dis* 2021;0:1–13. doi: 10.1136/annrheumdis-2020-219725

	RCTs	Prospective		Retrospective		Case Reports
		Controlled	Non controlled	Controlled	Non controlled	
Tocilizumab	4	18	13	36	39	28
Corticosteroids	6	14	0	24	10	11
Hydroxychloroquine	12	8	4	16	9	4
Convalescent plasma	3	6	5	4	10	14
Anakinra	1	0	0	4	4	10
Mesenchymal stem cells	0	1	3	0	1	8
Intravenous immunoglobulins	2	0	0	4	3	3
Baricitinib	1	3	0	1	1	0
Tocilizumab + glucocorticoids	0	3	1	0	1	1
Ruxolitinib	1	0	1	0	2	2
Interferon beta 2a	3	1	1	0	1	0
Colchicine	1	1	0	1	0	1
Sarilumab	0	1	2	0	0	0
Eculizumab	0	1	0	0	0	2
Leflunomide	2	0	0	0	0	0
Baricitinib + glucocorticoids	0	1	0	0	1	1
Mavrilimumab	0	1	0	0	0	0
Vilobelimab	1	0	0	0	0	0
Ruxolitinib + eculizumab	0	1	0	0	0	0
rhIL-7	0	1	0	0	0	1
Interferon alpha 2b	0	1	0	0	0	0
Interferon kappa	1	0	0	0	0	0
Infliximab	0	0	0	1	0	0
Canakinumab	0	0	0	0	1	1
Imatinib	0	0	0	0	0	1

Ruxolitinib+glucocorticoids	0	1	0	0	0	0
Anakinra + glucocorticoids	0	0	0	1	0	0
Cyclosporin + glucocorticoids	0	1	0	0	0	0
Lenzilumab	0	1	0	0	0	0
Itolizumab	0	0	1	0	0	0
AMY-101	0	0	0	0	0	1
Tesidolumab	0	0	0	0	1	0
Treg cells	0	0	0	0	0	1

The full list of references pertaining to articles included in the SLR but now shown in the main manuscript since better evidence was published is available upon request.

Online Supplementary Table S4. Characteristics of the randomized controlled trials included in the SLR.

			Patient characteristics		
Author	**Drug, dosage and administration, N**	**Comparator N**	**Patients hospitalized, oxygen therapy N(%)**	**NIV, N(%)**	**IMV, N(%)**
RECOVERY collaborative group	Dexamethasone 6 mg/d per os or iv N=2104	SOC N=4321	DEX 1279 (61%) SOC: 2604 (60%)	NA	DEX: 324 (15%) SOC: 683 (16%)
Prado Jeronimo et al	Methylprednisolone 0.5 mg/kg bid iv for 5d N=194	SOC+PBO N=199	88/393 (47.8)		133/393 (33.8)
Tomazini et al (CoDex)	Dexamethasone 20 mg/d iv for 5 d and then 10 mg/d iv for 5 d N=151	SOC[3] N=148	0	0	100%
Edalatifard et al	Methylprednisolone 250 mg/d^{-1} iv pulse for 3 d	SOC	MTP: 21 (61.8%) SOC: 17 (64.3%)	MTP: 13 (38.2%) SOC: 10 (35.7%)	0
Angus et al (REMAP-CAP)	Hydrocortisone 50 mg iv every 6 h for 7 d	SOC+PBO	0	HCT: 122 (45.6%) SOC: 48 (44.4%)	HCT: 173 (54.4%) SOC: 60 (63.6%)
Dequin et al (CAPE-COVID)	Hydrocortisone 200 mg/d for 4 d or 7 d; 100 mg/d for 2 d or 4 d; 50mg/d for 2 d or 3 d. Continuous iv infusion for 8 d or 14 d	SOC+PBO	0	HCT: 14 (18.4%) SOC: 14 (19.2%)	HCT: 62 (81.6%) SOC: 59 (80.8%)
Abd-Elsalam et al	HCQ 400 mg twice daily (in day 1) followed by 200 mg tablets twice daily	SOC[7] N=97	NR	NR	NR

	N=97				
Lyngbakken et al.	HCQ 400 mg twice daily for 7 days N=26	SOC[8] N=25	HCQ: 8 (29.6) SOC: 12 (46.2)	NR	NR
RECOVERY collaborative group	HCQ sulfate (in the form of a 200-mg tablet containing a 155-mg base equivalent) 800mg at baseline and at 6 hours, then 400 mg starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge N=1561	SOC[9] N=3155	HCQ: 938 (60.1) SOC: 1873 (59.3)		HCQ: 261 (16.7) SOC: 532 (16.9)
Cavalcanti et al.	HCQ 400 mg twice a day 7 days N=221	SOC[10] N=227 SOC[10] + azithromycin 500mg N=217	HCQ+AZT: 92 (42.4) HCQ: 89 (40.3) SOC: 97 (42.7)	0 (exclusion criteria)	0 (exclusion criteria)
Huang et al.	Chloroquine 500 mg orally twice daily for 10 days; N=10	SOC[11] N=12	NA	NA	NA
Tang et al.	HCQ 1200 mg daily for three days followed by a maintenance dose of	SOC[12] N=75	NA	NA	NA

	800 mg daily (total treatment duration: two or three weeks N=75				
Mirja et al.	HCQ (800 mg on day 1, followed by 400 mg once daily for 6 days N=136	SOC[13] N=157	0	0	0
Skipper et al.	HCQ 800mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) once daily for 4 more days (5 days in total). N=212	SOC[14]+PBO N=211	0	0	0
Omrani et al.	Oral HCQ (600 mg daily for one week), or oral HC plus oral AZ (500 mg day one, 250 mg daily on days two through five) N=152	SOC[15] + PBO (NA) N=152 SOC + AZT N=152	NA	0	0
Chen et al.	HCQ 400 mg twice for 1 day OR HCQ 200 mg twice daily for 6 days. N=21	SOC[16] N=12	0	0 (Exclusion criteria)	(Exclusion criteria)
Self et al.	HCQ 400 mg twice daily for 2 doses, then 200 mg twice daily for	SOC[17] + PBO N=237	46.8%	11.5%	6.7%

	8 doses N=242				
Ulrich et al.	HCQ 400 mg (2 tablets) by mouth 2 times per day (day 1) and 200 mg (1 tablet) by mouth 2 times per day (days 2–5) N=67	SOC[18] + PBO N=61	1%	1%	0 (exclusion criteria)
Hermine et al. (CORIMUNO-19-TOCI1)	TCZ, 8 mg/kg, IV plus usual care on day 1 and on day 3 if clinically indicated N=64	SOC[19] N=67	131 (100%) (>3L <15L)	0 (exclusion criteria)	0 (exclusion criteria)
Stone et al	TCZ 8mg/kg IV single dose N=161	SOC[20] N=81	NA	0 (exclusion criteria)	0 (exclusion criteria)
Salvarani et al.	TCZ 8mg/kg IV within 8 hours from randomization followed by a second dose after 12 hours. N=60	SOC[21] N=66	NA	0 (exclusion criteria)	0 (exclusion criteria)
Zhao et al.	TCZ IV 4−8 mg/kg (recommended 400 mg) N=5	SOC[22] + Favipiracvir N=7 SOC + Favipiracvir + TCZ N=14	NA	NA	NA
Mariette et al (CORIMUNO-19-ANA1)	Anakinra 200mg IV bid at day 1, 2 and 3, then 100mg bid at day4 and 100mg/day at day 5	SOC[23] N=55	114 (100%) (>3L <15L)	0 (exclusion criteria)	0 (exclusion criteria)

	In case of absence of improvement at D4: 400mg/day at day 4, 5, and 6, 200mg/day at day 7 and 100mg/day at day 8 N=59				
Cao et al.	Ruxolitinib 5mg bid N=22	SOC[24]+PBO N=21	RUXO: 18 (86) SOC: 18 (90)	RUXO: 3 (14) SOC: 2 (10)	0 (exclusion criteria)
Davoudi-Monfared et al Rahmani et al.	Interferon beta 250 mcg sc eod for 2w N=46	SOC[25] N=46	IFN: 26 (56) SOC: 22 (48	IFN: 1 (2) SOC: 0 (0)	IFN 15 (36) SOC 17 (44)
Monk et al.	Interferon beta (SNG001) 6 MIU delivered via nebulizer once daily for up to 14 days N=50	SOC[26]+PBO N=51	IFN= 28 (56%) SOC= 36 (75%)	IFN= 1 (2%) SOC= 1 (2%)	IFN=0 SOC=0
Gharebaghi et al	IVIG 5 gm5/d for 3d N=30	SOC[27, 28]+PBO N=29	NA	NA	NA
Tabarsi et al.	IGIV 400 mg/kg, IV, daily for three days N=52	SOC[29]+PBO N=32	N=84	NA	NA
Vlaar et al	Vilobelimab 800mg/d iv up to seven doses N=15	SOC[30] N=15	VILO: N=7 (47) SOC= N=8 (53)		VILO: N= 5 (25) SOC: N=10 (75)
Wang et al.	Leflunomide 50 mg, q12h three consecutive times, after	SOC[31] N=24	NA	NA	NA

	20 mg/d for 10d N=24				
Hu et al.	Leflunomide 50 mg, q12h three consecutive times, after 20 mg/d for 10d N=5	SOC[32] N=5	NA	0 (exclusion criteria)	0 (exclusion criteria)
Deftereos et al.	Colchicine Loading dose 1.5 mg followed by 0.5 mg 60min later. Maintenance 0.5mg bid for a maximum of 21 d N=50	SOC[33] N=55	COL: N= 36 (65) SOC: N=30 (60)	COL: N=0 SOC: N=3 (6)	COL N=0 SOC N=0
WHO Solidarity Trial Consortium	HCQ four tablets at hour 0, four tablets at hour 6, and, starting at hour 12, two tablets twice daily for 10 days N=954 INTERFERON Beta 1 mainly SC 3 doses over a period of 6 days (the day of randomization and days 3 and 6) of 44 µg N=2063	SOC[34] N=4088	N=3200 HCQ=345 IFN=482	N=7146 HCQ=517 IFN=1429	N=916 HCQ=85 IFN=139
Simonovic et al. 2020	Convalescent plasma 1 infusion Titer >1:800 N=228	SOC[35]+ 1 Administration of placebo (saline solution)	NA	ICU without precision N=67 Convalescent plasma N=25 Placebo	

		N=105			
Li et al. 2020	Convalescent plasma 1 infusion 4 to 13 mL/kg of recipient body weight N=52	SOC[36] N=51	Convalescent plasma N=15 Placebo N=15	Convalescent plasma N=21 Placebo N=23	Convalescent plasma N=14 Placebo N=11
Agarwal et al. 2020	Convalescent plasma 2 doses of 200mL 24hours appart N=235	SOC[37] N=229	PLASMA N=235 SOC N=229	0 (exclusion criteria)	0 (exclusion criteria)
Kalil et al. 2020	Baricitinib 4 mg/day for 14 days or until hospital discharge + Remdesivir 200mg on day 1 followed by 100mg/day through 10d or until hospital discharge or death N=515	Remdesivir 200mg on day1 followed by 100mg/day through 10d or until hospital discharge or death + PBO + SOC[38] N=518	BARI+RDV N=288 (55.9) RDV N= 276 (53.3) INTERVENTION -Oxygen therapy 56% -NIV (including HFO) 20% -MIV 10% COMPARATOR - Oxygen therapy 53% -NIV (including HFO) 22% -MIV 11%	BARI+RDV N=103 (20.0) RDV N= 113 (21.8)	BARI+RDV N=54 (10.5) RDV N= 57 (11.0)
Fu et al. 2020	Interferon kappa 2mg in 5 mL sterilized water also containing 5mg of trefoil factor 2 delivered for 20-30 min by a nasal mask from the first day of hospitalization 6 times every 24 h N=40	SOC[39] N=40	0	0	0
Salama et al.	TCZ IV 8mg/kg one or two doses N=249	SOC[40]+PBO N=128	TCZ= 161 SOC= 81	TCZ=64 SOC=36	0 (exclusion criteria)

1: The current standard care for Covid-19 was at the discretion of the treating physicians. 0 to 3% of patients received hydroxychloroquine, lopinavir–ritonavir, or interleukin-6 antagonists; 2: Current standard care + intravenous ceftriaxone (1g 2x for 7 days) plus azithromycin (500 mg 1x for 5 days) or clarithromycin (500 mg 2x for 7 days), starting on day 1; 3: The current standard care for Covid-19 was at the discretion of the treating physicians; 4: Standard care (Hydroxychloroquine sulfate, Lopinavir, and Naproxen); 5: All patients meeting ARDS criteria used preemptive intravenous ceftriaxone (1 g 2× for 7 days) plus azithromycin (500 mg 1× for 5 days) or clarithromycin (500 mg 2× for 7 days), starting on Day 1; 6: The current standard care for Covid-19 was at the discretion of the treating physicians. 0 to 3% of patients received hydroxychloroquine, lopinavir–ritonavir, or interleukin-6 antagonists; 7: NA, 8: NA; 9: paracetamol, oxygen, fluids (according to assessment), empiric antibiotic (cephalosporins), oseltamivir if needed (75 mg/12 hours for 5 days), and hydrocortisone for severe cases. 10: The current standard care for Covid-19 was at the discretion of the treating physicians. The use of glucocorticoids, other immunomodulators, antibiotic agents, and antiviral agents was allowed; 11: Paracetamol, oxygen, fluids (according to assessment), empiric antibiotic (cephalosporins), oseltamivir if needed (75 mg/12 hours for 5 days), and hydrocortisone for severe cases. 12: NA; 13: NA, 14: Skipper None; 15 NA; 16 The treatment consisted of: (1) ceftriaxone 2 g daily for 7 days ± azithromycin 500 mg on day 1 and 250 mg on days 2–5; or (2) levofloxacin 750 mg daily for 5 d; or (3) levofloxacin 500 mg daily; or (4) moxifloxacin 400 mg daily for 7–14 days for subjects allergic to ceftriaxone or azithromycin or according to physician discretion. Oseltamivir 75 mg b.i.d. was administered for 5 days to subjects presenting with concomitant influenza A or B infection); 17 NA; 18 NA; 19: Usual care included antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants; 20: Some patients received remdesivir as concomitant treatment, whereas no patients received dexamethasone. Antiviral therapy, hydroxychloroquine, and glucocorticoids were permitted as concomitant treatment; 21: Patients in the control arm received supportive care following the treatment protocols of each center. All drugs were allowed but IL-1 blockers, Jak inhibitors, and tumor necrosis factor inhibitors. Steroids were allowed if already taken before hospitalization. In case of occurrence of documented clinical worsening, patients randomized in both arms could receive any therapy, including steroids, and, for patients randomized in the control arm, tocilizumab. 22 NA; 23: antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the clinicians. 24: SoC treatment included antiviral therapy, supplemental oxygen, noninvasive and invasive ventilation, corticosteroid, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation. 25: HCQ+lopinavir/ritonavir or atazanavir-ritonavir. Based on patients' clinical conditions, azithromycin, intravenous ascorbic acid, antibiotics, intravenous immunoglobulin (IVIG), or a corticosteroid, was added to the antiviral regimens; 26 NA; 27: Lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days. Other supportive cares such as fluid therapy, stress ulcer prophylaxis, deep vein thrombosis, treatment of electrolyte disorders and antibiotic therapy were considered according to the hospital protocols. 28: At least both one antiviral and one chloroquine-class drug; 29: hydroxychloroquine, lopinavir/ritonavir and supportive care;30: Including but not limited to lung protective ventilation, thrombosis prophylaxis, renal replacement therapy when indicated, and access to advanced therapies including extracorporeal membrane oxygenation. Hydroxychloroquine was allowed during the study; active concomitant treatment with antiviral or other immunomodulatory drugs was not allowed. 31: nebulized IFN-α-2a alone for 10 days; 32:supportive treatment (Arbidol, Lianhua Qingwen Capsule, Magnesium Isoglycyrrhizinate, and Cefoperazone); 33: HCQ and/or lopinavir/ritonavir and/or IV dexamethasone. 34: NA; 35: Patients were allowed to receive antiviral agents, glucocorticoids, or both according to the standard of care at the provider health care institution.36: Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medication. 37: followed by the participating clinical sites for the management of patients with covid-19 included antivirals (hydroxychloroquine, remdesivir, lopinavir/ritonavir, oseltamivir), broad spectrum antibiotics, immunomodulators (steroids, tocilizumab), and supportive management. 38 Venous thromboembolism prophylaxis was recommended for all the patients without a major contraindication. If a hospital had a written policy for Covid-19 treatments, patients could receive those treatments. In the absence of a written policy, other experimental treatment and off-label use of marketed medications intended as specific treatment for Covid-19 were prohibited. This included glucocorticoids, which were permitted only for standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome. 39 Standard care included symptomatic treatment with hydroxychloroquine, antibiotic agents, vasopressors, antifever medicine, vitamin C, immune enhancers, or traditional Chinese medicines. 40 Standard care according to local practice, which could include antiviral treatment, the limited use of systemic glucocorticoids (recommended dose, ≤1 mg per kilogram of body weight of methylprednisolone or equivalent), and supportive care.

Online Supplementary Table S5. Effect of immunomodulatory drugs assessed by prospective studies on mortality, invasive and non-invasive ventilation and on oxygen support in severe COVID-19

Online Supplementary Text S7

List of abbreviations

Outcome	Drug	Author, year [ref]	Study groups	Results	RoB
Mortality	**Mavrilimumab**	De Luca et al. 2020	MAV+SOC vs SOC	No difference in mortality (p=0.086)	Unclear
	Sarilumab	Della Torre et al. 2020	SARI+SOC vs SOC	No difference between groups in death rate	High
	rhIL-7	Laterre et al. 2020	IL-7+SOC vs SOC	30-day mortality did not differ between groups	High
	Eculizumab	Annane et al 2020	ECU+SOC vs SOC	Significant difference in survival curves between groups (P = 0.04)	Unclear
	Tocilizumab + glucocorticoids	Ramiro et al 2020	SOC+TCZ+MTP vs SOC	At day 14, 38% vs 12% (p<0.0001) HR of mortality 0.26 (0.13 to 0.52) (multivariable)	Unclear
		Martínez-Urbistondo et al 2020	SOC+Early TCZ+MTP vs SOC+Standard TCZ+MTP	Survival ET: RR 0.18, p 0.01 and HR 0.13, p 0.01	High
		Sanz Herrero et al. 2020	SOC + TCZ+ MTP vs SOC+ TCZ	RR for mortality in favor of combination 0.20, 95% CI: 0.08–0.47, P < 0.01.	High
	Baricitinib + glucocorticoids	Rodriguez Garcia	SOC+ BARI+MTP vs SOC + MTP	No significant differences between CS and BARI+CS	High
	Ruxolitinib + eculizumab	Giudice et al. 2020	RUXO+ECU+SOC VS SOC	No differences between groups	High
	Cyclosporin + glucocorticoids	Galvez-Romero et al. 2020	SOC+CSA+MTP SOC+MTP	The mortality in the CsA group was 22% compared to 35% in the control group (p=0.02)	High
Non-invasive or invasive mechanical ventilation	**Mavrilimumab**	De Luca et al. 2020	MAV+SOC vs SOC	No difference in need of MV (p=0.14)	Unclear
	Sarilumab	Della Torre et al. 2020	SARI+SOC vs SOC	No difference between groups in the need of MV and time to MV	High
	Lenzilumab	Temesgen et al 2020	LEN+SOC vs SOC	No difference in ventilator-free survival between groups	High
	Eculizumab	Annane et al 2020	ECU+SOC vs SOC	In patients who were ventilated at baseline no difference in the number of days free of mechanical ventilation at day 15	Unclear
	Tocilizumab + glucocorticoids	Ramiro et al 2020	SOC+TCZ+MTP vs SOC	28% vs 12% p=0.0003 HR of mechanical ventilation 0.22 (0.10 to 0.52)	Unclear
	Ruxolitinib + eculizumab	Giudice et al. 2020	RUXO+ECU+SOC VS SOC	None of the patients on the treated arm required invasive mechanical ventilation or high-flow nasal oxygenation after or during treatment	High
Oxygen support	**Tocilizumab + glucocorticoids**	Ramiro et al 2020	SOC+TCZ+MTP vs SOC	53% vs 29% (p=0.0003); HR for becoming independent from oxygen support 2.36 (1.45 to 3.83)	Unclear
	Baricitinib + glucocorticoids	Rodriguez Garcia et al. 2020	SOC+ BARI+MTP vs SOC + MTP	Lower proportion of patients required supplemental oxygen both at discharge and 1month later in BARI+CS vs CS. The proportion of patients requiring supplemental oxygen at discharge and 1 month later was similar in BARI low dose vs high dose	High

ARDS, acute respiratory distress syndrome

CI, confidence interval

COVID-19, coronavirus disease 2019

CoV-2, coronavirus 2

DEX, dexamethasone

HCQ, hydroxychloroquine

HCT, hydrocortisone

HLH, haemophagocytic lymphohistocytosis

HR, hazard ratio

IFN, interferon

IMV, invasive mechanical ventilation

IVIg, intravenous immunoglobulins

JAK, Janus kinase

MAS, macrophage activation syndrome

MTP, methylprednisolone

OR, odds ratio

PICO, population intervention comparator and outcome

Alunno A, *et al. Ann Rheum Dis* 2021;0:1–13. doi: 10.1136/annrheumdis-2020-219725

PtC, points to consider

RCT, randomized controlled trial

RMDs, rheumatic and musculoskeletal diseases

RoB, risk of bias

SARS, severe acute respiratory syndrome

SLR, systematic literature review

SOC, standard of care

TCZ, tocilizumab

Alunno A, *et al. Ann Rheum Dis* 2021;0:1–13. doi: 10.1136/annrheumdis-2020-219725