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

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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

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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.

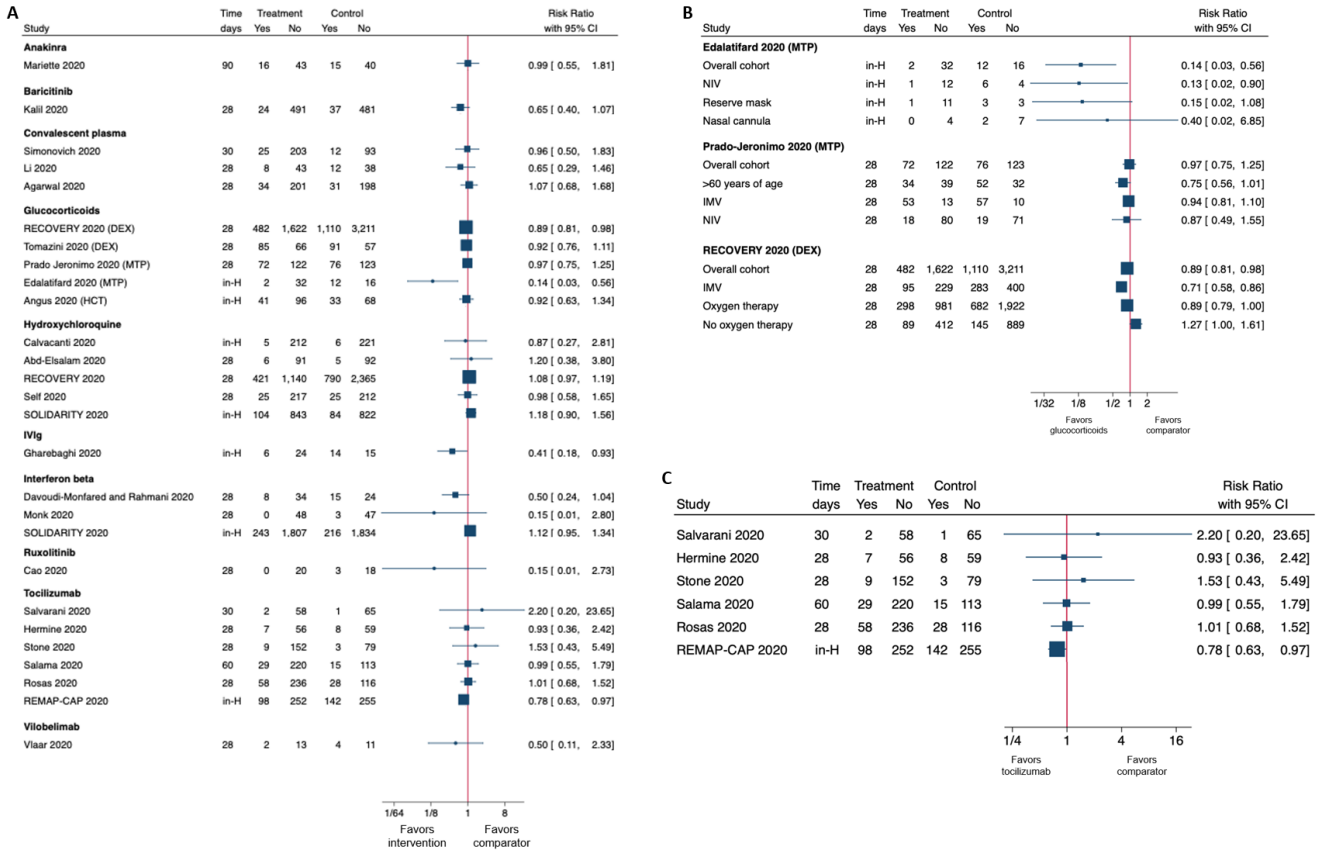

Figure 1 Forest plots showing the risk ratio (RR) and 95% CI for mortality in randomised controlled trials divided by intervention. The latest follow-up available is reported in the timing column. Panel A shows RRs in overall cohorts, panel B shows overall cohorts and subgroup analysis in studies assessing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

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