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Immunomodulatory therapies for the treatment of SARS-CoV-2 infection: an update of the systematic literature review to inform EULAR points to consider

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ABSTRACT

Objective To update the EULAR 2020 systematic literature review (SLR) on efficacy and safety of immunomodulatory agents in SARS-CoV-2 infection.

Methods As part of a EULAR taskforce, a systematic literature search update was conducted from 11 December 2020 to 14 July 2021. Two reviewers independently identified eligible studies and extracted data on efficacy and safety of immunomodulatory agents used therapeutically in SARS-CoV-2 infection at any stage of disease. The risk of bias (RoB) was assessed with validated tools.

Results Of the 26 959 records, 520 articles were eligible for inclusion. Studies were mainly at high or unclear RoB. New randomised controlled trials (RCTs) on tocilizumab clarified its benefit in patients with severe and critical COVID-19, mainly if associated with glucocorticoids. There are emergent data on the usefulness of baricitinib and tofacitinib in severe COVID-19. Other therapeutic strategies such as the use of convalescent plasma and anti-SARS-CoV-2 monoclonal antibodies showed efficacy in subjects not mounting normal anti-SARS-CoV-2 antibody responses.

Conclusion This new SLR confirms that some immunomodulators (tocilizumab and JAK inhibitors) have a role for treating severe and critical COVID-19. Although better evidence is available compared with the previous SLR, the need of RCT with combination therapy (glucocorticoids+anti-cytokines) versus monotherapy with glucocorticoids still remains alongside the need for standardisation of inclusion criteria and outcomes to ultimately improve the care and prognosis of affected people. This SLR informed the 2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19.

Key messages

What is already known about this subject?

- Several compounds with immunomodulatory activity have been tested in patients with SARS-CoV-2 infection at various stages of the disease.
- Randomised controlled trials (RCTs) are available only for a few immunomodulatory compounds/strategies, sometimes with conflicting results, and mostly for moderate to severe/critical COVID-19.

What does this study add?

- By updating the previous systematic literature review (SLR), all the new RCTs published up until July 2021 were collected. The efficacy of glucocorticoids and tocilizumab in severe and critical COVID-19 was clarified and potentially new promising therapeutic approaches were described.
- There are emergent data on the usefulness of baricitinib and tofacitinib in severe COVID-19, mainly if associated with glucocorticoids.
- Other therapeutic strategies such as the use of convalescent plasma and anti-SARS-CoV-2 monoclonal antibodies seem to be useful only in selected subgroups of patients.

How might this impact on clinical practice or further developments?

- This SLR informed the 2021 update of the EULAR points to consider for the use of immunomodulatory therapy in COVID-19.

INTRODUCTION

The SARS-CoV-2 pandemic has challenged the global healthcare system. Severe COVID-19 pneumonia is associated with inflammation and immunothrombosis that may be treatable with immunomodulatory therapies but optimal treatment and timing is incompletely understood. Our previous systematic literature review (SLR)[1] noted that despite the extremely large number of available studies, randomised controlled trials (RCTs) were few and most articles were of

lower level of evidence and at high risk of bias (RoB). Data on efficacy (or lack thereof) of some compounds such as hydroxychloroquine (HCQ) were consistent across studies; however, for other drugs, such as tocilizumab (TCZ), both positive and negative results were reported without a strong signal in either direction.[1] Furthermore, data emerging from the 'grey literature', either in full as preprints or in part via press releases, added a layer of complexity underscoring the evolving nature of COVID-19 where contradictory findings were often reported.

Since new studies are continuously published, overarching institutions regularly update their recommendations for the management of COVID-19.[2 3] Similarly, we conducted an update of our SLR in order to inform the 2021 update of the EULAR points to consider for the use of immunomodulatory therapy in COVID-19.

METHODS

Search methodology

Based on the same research questions of the original SLR and using the same systematic search strategy,[1] a search was performed in MEDLINE, Embase, The Cochrane Database of Systematic Reviews, CENTRAL and CINAHL. The search was conducted from 11 December 2020 (cut-off date of the previous SLR) to 14 July 2021. 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', restricted to RCT not yet published in peer-reviewed 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 points to consider. We also conducted a new search to explore the efficacy and safety of anti-SARS-CoV-2 monoclonal antibodies (mAbs) in infected subjects up to 14 July 2021 (online supplemental text 1).

Study selection, data collection and assessment of RoB

Original research articles of any study design, published in English, in peer-reviewed journals, addressing adults with proven SARS-CoV-2 infection treated with one or more immunomodulatory agent or with anti-SARS-CoV-2 mAbs, were eligible. Two reviewers (AA and AN) independently assessed titles and abstracts according to the predetermined eligibility criteria, followed by full-text review. Discrepancies were resolved by discussion and the task force methodologist (PMM) was consulted in the case of uncertainties. Data on patient characteristics, investigated drug and administration scheme, and comparators and outcomes were extracted, as in the previous SLR. Whenever possible, risk ratios (RRs) and corresponding CIs were calculated. The RoB was assessed using validated tools.

RESULTS

Of the 26 959 records yielded by the search on immunomodulatory therapies, 711 were selected for full-text review and 3 additional articles were identified by handsearch. Of these, 520 articles on 33 therapeutic strategies met the inclusion criteria (online supplemental tables 1 and 2). Robust evidence was mostly available for moderate-to-severe/critical COVID-19.

Of the 275 records yielded by the search on anti-SARS-CoV-2 mAbs, 39 were selected for full-text review and 19 met the inclusion criteria (online supplemental table 3). The best evidence available for each compound is shown.

RCT data in patients with moderate to severe/critical COVID-19

A total of 37 RCTs, all at high or unclear RoB, evaluating 14 therapeutic approaches in severe/critical COVID-19 were retrieved by the SLR (online supplemental table 4).

Antimalarials

Eleven new RCTs were retrieved by the SLR search update, adding to the existing eight RCTs on HCQ included in the previous SLR. Out of these 11 new studies, 4 have been stopped early for futility,[4–7] 2 have been stopped for harmful effects of one or several compounds in the intervention arms,[8 9] and 1 is underpowered,[10] hence the results are not described in this manuscript. Out of the six studies that included patients with moderate to severe COVID-19, one compared HCQ to chloroquine or ivermectine showing no efficacy on death, progression to invasive mechanical ventilation (IMV) or admission to intensive care unit (ICU) at day 90.[11] The second study explored the efficacy and safety of adding either HCQ, lopinavir-ritonavir or a combination of the two to standard of care (SOC) in critically ill patients.[12] One of the major findings of this trial is a significant reduction of survival in all three intervention arms compared with SOC (OR 0.65, 95% CI 0.45 to 0.95; OR 0.56, 95% CI 0.30 to 0.89; and OR 0.36, 95% CI 0.17 to 0.73, respectively), suggesting a harmful role of lopinavir-ritonavir and HCQ (tables 1 and 2).

Glucocorticoids

Three new RCTs on glucocorticoids (GCs) were retrieved by the SLR update. Unfortunately, all three studies failed to recruit the target number of subjects allowing the trials to be sufficiently powered and therefore were interrupted early and no conclusion could be drawn from the results.[13–15]

IL-6R inhibitors

The search update retrieved seven new RCTs on tocilizumab (TCZ)[16–22] including COVACTA,[18] REMAP-CAP,[19] RECOVERY,[20] EMPACTA[22] and the post hoc analysis of the CORIMUNO-TOCI-1 trial at day 90 on the subgroup

Table 1 Effect of immunomodulatory therapies on mortality. Results from randomized controlled trials in moderate to severe and critical COVID-19.

Drug	Author (ref)	Intervention comparator(s)	Timepoint (days)	N treated	N (%) death	RR (95% CI)	RoB
Hydroxychloroquine	Galan *et al*[11]	HCQ+SOC	90	168	14 (22.2)	0.97 (0.5 to 1.9)*	High
		CQ+SOC		61	13 (21.3)		
		Ivermectin+SOC		53	12 (23)		
	REMAP-CAP[12]	HCQ +SOC	in-H	49	17 (35)	1.16 (0.76 to 1.75)†	Unclear
		Lopinavir-ritonavir +SOC		249	88 (35)		
		Lopinavir-ritonavir +HCQ + SOC		26	13 (50)		
		SOC		353	106 (30)		
Tocilizumab	CORIMUNO-TOCI-1[21]	TCZ+SOC	90	64	7 (11)	0.67 (0.28 to 1.61)	Unclear
		SOC		67	11 (18)		
	CORIMUNO-TOCI-1 (CRP >150 mg/L)[21]	TCZ+SOC	45	22	2 (9)	0.26 (0.06 to 1.10)	Unclear
		SOC		23	8 (35)		
	RECOVERY[20]	TCZ+SOC	28	2094	621 (31)	0.82 (0.75 to 0.90)	Unclear
		SOC		2022	729 (35)		
	REMAP-CAP[19]	TCZ+SOC	21	353	98 (28)	0.79 (0.63 to 0.97)	Unclear
		SOC		402	142 (36)		
	COVACTA[18]	TCZ+SOC	28	294	58 (20)	1.01 (0.7 to 1.5)	Unclear
		PBO+SOC		144	28 (20)		
	EMPACTA[22]	TCZ+SOC	28	249	26 (10)	1.22 (0.85 to 1.73)	Unclear
		PBO+SOC		128	11 (9)		
Sarilumab	Lescure *et al*[23]	SARI200 +SOC	60	159	19 (11)	1.13 (0.5 to 2.4)	Unclear
		SARI400 +SOC		173	18 (10)	0.98 (0.5 to 2.1)	
		PBO+SOC		84	9 (11)		
	REMAP-CAP[19]	SARI+SOC	21	42	10 (22)	0.71 (0.58 to 0.86)	Unclear
		SOC		402	142 (36)		
Canakinumab	CAN-COVID[27]	CANAK+SOC	29	223	11 (5)	0.68 (0.32 to 1.44)	Unclear
		PBO+SOC		222	16 (7)		
Colchicine	Lopes *et al*[28]	COL+SOC	7	36	0 (0)	–	High
		PBO+SOC		36	2 (5)		
Tofacitinib	Guimarães *et al*[30]	TOFA+SOC	28	144	4 (3)	0.49 (0.15 to 1.63)	Unclear
		PBO+SOC		145	8 (5)		
Mavrilimumab	Cremer *et al*[36]	MAV+SOC	60	21	1 (5)	0.23 (0.03 to 1.8)	High
		SOC		19	4 (21)		

Continued

Table 1 Continued

Drug	Author (ref)	Intervention comparator(s)	Timepoint (days)	N treated	N (%) death	RR (95% CI)	RoB
Interferon beta	Darazan *et al*[40]	IFNbeta1a+SOC	21	20	4 (20)	0.4 (0.2 to 1.2)	High
		IFNbeta1b+SOC		20	6 (30)	0.7 (0.3 to 1.5)	
		SOC		20	9 (45)		
	Khamis *et al*[41]	IFNbeta +favipiravir	in-H	44	5 (11)	0.8 (0.3 to 2.6)	High
		HCQ		45	6 (13)		
Convalescent plasma	Balcells *et al*[42]	Early CP +SOC	14	28	5 (18)	2.68 (0.56 to 12.71)	High
		Differed/no CP+SOC		30	2 (7)		
	Pouladzadeh *et al*[44]	CP+SOC	30	30	3 (10)	0.60 (0.16 to 2.29)	High
		SOC		30	5 (17)		
Non-SARS-CoV-2 IVIG	Raman *et al*[46]	IVIG+SOC	28	50	0 (0)	–	High
		SOC		50	1 (2)		

Results from randomised controlled trials in moderate to severe and critical COVID-1.
Relative risks are unadjusted and calculated by the authors using the data provided in the articles.
*HCQ vs IVE.
†HCQ vs SOC.
CANAK, canakinumab; COL, colchicine; CP, convalescent plasma; CQ, chloroquine; HCQ, hydroxychloroquine; IFN, interferon; IVIG, intravenous immunoglobulins; MAV, mavrilimumab; PBO, placebo; RoB, risk of bias; RR, relative risk; SARI, sarilumab; SOC, standard of care; TCZ, tocilizumab; TOFA, tofacitinib.

Table 2 Effect of immunomodulatory therapies on ventilation. Results from randomized controlled trials in moderate to severe and critical COVID-19.

Drug	Author (ref)	Intervention comparator(s)	Timepoint (days)	N treated	Results	RoB
Hydroxychloroquine	Galan *et al*[11]	HCQ+SOC CQ+SOC Ivermectin+SOC	90	168 61 53	Patients requiring IMV 13 (21) 12 (21) 13 (23) HCQ vs IVE RR (95% CI) 0.83 (0.4 to 1.6)	High
Tocilizumab	Mariette *et al*[21]	TCZ+SOC SOC	90	64 67	IMV or death, subgroup CRP>15 mg/dL, 18% 57% HR (95% CI) 0.18 (0.06 to 0.59)	Unclear
	RECOVERY[20]	TCZ+SOC SOC	28	2094 2022	Non-IMV subgroup progression to IMV or death 35% 42% RR (95% CI) 0.84; 0.77 to 0.92	Unclear
	REMAP-CAP[19]	TCZ+SOC SOC	21	353 402	CV and respiratory organ support-free days OR (95% credible interval) 1.64 (1.25 to 2.14)	Unclear
	COVACTA[18]	TCZ+SOC PBO+SOC	28	294 144	Clinical status on 7-point ordinal scale −1.0; 95% CI −2.5 to 0; p=0.31	Unclear
	EMPACTA[22]	TCZ+SOC PBO+SOC	28	249 128	Progression to IMV or death: HR (95% CI) 0.56 (0.33 to 0.97)	Unclear
Sarilumab	Lescure *et al*[23]	SARI 200 +SOC SARI 400 +SOC PBO+SOC	60	159 173 84	Need of NIV/IMV 26 (20); RR (95% CI) 1.06 (0.6 to 1.9); 33 (30); RR (95% CI) 1.2 (0.7 to 2.2) 13 (19)	Unclear
	REMAP-CAP[19]	SARI+SOC SOC	21	42 402	CV and respiratory organ support-free days OR (95% credible interval) 1.76 (1.17 to 2.91)	Unclear
Canakinumab	CAN-COVID[27]	CANAK+SOC PBO+SOC	29	223 222	Patients alive not requiring IMV 198 (89) 191 (86) p=0.29	Unclear
Colchicine	Lopes *et al*[28]	COL+SOC PBO+SOC	7	36 36	Need of oxygen therapy 3 (9) 15 (42) RR (95% CI) 0.2 (0.06 to 0.63)	High
Tofacitinib	Guimarães *et al*[30]	TOFA+SOC PBO+SOC	28	144 145	Death or respiratory failure 26 (18) 42 (29) RR (95% CI) 0.63 (0.4 to 0.97)	Unclear
Mavrilimumab	Cremer *et al*[36]	MAV+SOC SOC	60	21 19	Need of IMV 5 (24) 4 (21) RR (95% CI) 1.13 (0.3 to 3.6)	High
Interferon beta	Darazan *et al*[40]	IFNbeta1a+SOC IFNbeta1b+SOC SOC	21	20 20 20	IMV 7 (35%) in each of the three patient groups	High
Convalescent plasma	Balcells *et al*[42]	Early CP +SOC Differed/no CP+SOC	14	28 30	IMV 5 (18) 2 (7) RR (95% CI) 3.04 (0.54 to 17.17)	High
Non-SARS-CoV-2 IVIG	Raman *et al*[46]	IVIG+SOC SOC	28	50 50	Days on IMV, mean (SD) 2.4 (0.9) 4.5 (2.7) p=0.01	High

Results from randomised controlled trials in moderate to severe and critical COVID-19.
CANAK, canakinumab; COL, colchicine; CP, convalescent plasma; CQ, chloroquine; CRP, C reactive protein; CV, cardiovascular; HCQ, hydroxychloroquine; IFN, interferon; IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulins; MAV, mavrilimumab; NIV, non-invasive ventilation; PBO, placebo; RoB, risk of bias; RR, relative risk; SARI, sarilumab; SOC, standard of care; TCZ, tocilizumab; TOFA, tofacitinib.

of patients with C reactive protein (CRP) >150 mg/L.[21] Among these studies, REMAP-CAP[19] (n=353 TCZ +SOC, n=42 SARI+SOC, n=402 SOC) RECOVERY[20] (n=2094 TCZ +SOC group and n=2022 in SOC group) and the post hoc analysis of CORIMUNO-TOCI-1[21] (n=64 TCZ +SOC and n=67 SOC) showed a reduction of death

at Day 28 (RR 0.82, 95% CI 0.75 to 0.90), day 21 (RR 0.27, 95% CI 0.12 to 0.72) and day 90 (CORIMUNO-TOCI-1 in patients with CRP >150 mg/L), respectively (RR 0.64, 95% CI 0.25 to 1.65). Of note, in all these studies except the post hoc analysis of CORIMUNO-TOCI-1,[21] where patients received only oxygen between 3 and 15 L, at baseline the patients were receiving oxygen (26% to 46%), NIV (31% to 48%) or MV (5%–30%). In addition to the efficacy on death, reduction of progression to MV or death at day 21[20] or day 90[21] in CORIMUNO-TOCI-1 in patients with CRP >150 mg/L or an increase in cardiovascular or respiratory support-free days[19] were observed. COVACTA[18] comparing TCZ +SOC (n=294) to PBO+SOC (n=144) did not show any efficacy on death at day 28 (RR 1.01, 95% CI 0.7 to 1.5) or improvement of clinical outcome (RR 1.01, 95% CI 0.7 to 1.5). The study from Soin *et al*[16] did not show efficacy on death or disease progression at day 14 or day 28.

Of note, all studies except Soin *et al* were evaluated at unclear RoB. One study was underpowered and therefore results are not detailed.[17]

The evidence regarding sarilumab is scarcer as the search retrieved two RCTs at unclear RoB; one comparing sarilumab to SOC,[19] and the other comparing sarilumab to PBO.[23] The REMAP-CAP trial[19] included a small arm comparing sarilumab (n=44 patients) to SOC (n=402); most patients in the sarilumab arm were receiving NIV (48%) at baseline. The study showed a reduction in death and CV and respiratory organ support-free days (RR 1.76, 95% CI 1.17 to 2.91).[18] The other RCT[23] compared two dosages of sarilumab (200 and 400 mg) to PBO, and showed no efficacy on death (Sari 200: RR 1.13, 95% CI 0.5 to 2.4; Sari 400: RR 0.98, 95% CI 0.5 to 2.1), progression to MV (Sari 200: RR 1.06, 95% CI 0.6 to 1.9; Sari 400: RR 1.2, 95% CI 0.7 to 2.2) or admission to ICU (Sari 200: RR 0.83, 95% CI 0.3 to 2.1; Sari 400: RR 1.2, 95% CI 0.5 to 2.7).

Of note, there is a high heterogeneity among trials in terms of the proportion of patients receiving GCs as part of SOC. An important difference was observed between trials starting before and after the positive results of the GC arm of the RECOVERY trial.[24] It is noteworthy that while in two positive RCTs, a high percentage of patients were receiving GCs (82% to 93%),[19 20] in an important negative trial, COVACTA,[18] which failed to show efficacy in reducing death or improving clinical status, only up to 50% of patients were receiving GCs. In addition, a recent RCT meta-analysis published in JAMA concluded that TCZ reduced all-cause mortality (OR 0.83, 95% CI 0.72 to 0.94) and progression to MV, ECMO or death (OR 0.74, 95% CI 0.66 to 0.82) at day 28.[25]

Of interest, when analysing the subgroup of patients receiving GCs compared with those who did not, death at day 28 was only significantly reduced in the TCZ group receiving GCs (RR 0.77, 95% CI 0.68 to 0.87) p=0.008) but neither in the TCZ group not receiving GCs (RR 1.06, 95% CI 0.85 to 1.33) nor in the SARI group regardless of their GCs status (RR 0.77, 95% CI 0.64 to 1.31, p=0.34).

IL-1 inhibitors

As far as anakinra in concerned, only one study at high RoB was retrieved by the search update. This corresponded to a preprint that was subsequently published during the preparation of this manuscript.[26] This study included patients with COVID-19 pneumonia and soluble urokinase plasminogen activator elevations at 6 ng/mL or above, which is considered as a predictor of unfavourable outcome. In this population, anakinra 100 mg subcutaneous for 7–10 days increased the number of patients recovered (RR 1.9, 95% CI 1.5 to 2.5), according to the WHO 11-point clinical progression ordinal scale, and decreased mortality at day 28: 3.2% vs 6.9% (HR=0.45, p=0.045).

Regarding canakinumab, no RCT was retrieved by the search update but while writing this manuscript the CAN-COVID study was published[27] and it demonstrated that the addition of canakinumab to SOC did not provide any benefit on survival at 29 days.

Colchicine

The SLR identified one small RCT at high RoB.[28] The study reported that colchicine 0.5 mg three times per day for 5 days followed by 0.5 mg two times per day for 5 days in addition to SOC was able to reduce the duration of hospitalisation and the need of oxygen therapy. However, no significant effect was observed with regard to admission to ICU. In addition, it is important to mention that the colchicine arm of the RECOVERY trial closed in March 2021 since an interim analysis demonstrated no convincing evidence that further recruitment would provide conclusive evidence of benefit in any prespecified subgroup.[29]

JAK inhibitors

One RCT[30] comparing tofacitinib or placebo in addition to SOC reported a significant improvement of the composite outcome of respiratory failure or mortality at day 28 (RR 0.63, 95% CI 0.41 to 0.97) in a population where the large majority of patients (about 90%) received GCs as part of SOC.

Regarding baricitinib, the SLR retrieved no RCT but important information emerged from the grey literature. The addition of baricitinib to SOC, where the large majority of patients received GC as part of SOC, proved ineffective in improving the composite outcome of progression to NIV/IMV or death by day 28 (OR 0.85, 95% CI 0.67 to 1.08; p=0.18) (COV-BARRIER trial published as a preprint on 3 May 2021 and subsequently published in a peer-reviewed journal while preparing this manuscript).[31] However, the study found a decrease of 28-day all-cause mortality: 8% vs 13% (HR 0.57; 95% CI 0.41 to 0.78; p=0.0018). Finally, with regard to the combination of baricitinib and remdesivir, the Fourth iteration of the Adaptive COVID-19 Treatment Trial (ACTT-4) comparing baricitinib +remdesivir+placebo versus remdesivir +dexamethasone+placebo met predefined futility criteria in an interim analysis hence closed enrolment in

April 2021. This was announced by a press release and interim data are not available.[32]

A small multiple ascending dose study of the inhaled pan-JAK inhibitor nezulcitinib provided encouraging, although not significant results, on mortality and progression to IMV in hospitalised patients with COVID-19 requiring oxygen therapy and receiving GC as part of SOC.[33] Nezulcitinib 3 mg is currently under investigation in a larger trial.[34] No new RCT data on other JAKs were retrieved but the negative RUXCOVID trial data were published on 21 June 2021 on clinicaltrials.gov website and demonstrated that the addition of ruxolitinib to SOC did not provide any benefit on any clinical outcome at day 28.[35]

GM-CSF inhibitors

In the previous SLR, no RCTs on granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibitors were identified. The update allowed identifying a small RCT investigating mavrilimumab in addition to SOC in hospitalised patients with COVID-19 receiving oxygen therapy or NIV but not IMV.[36] This study did not provide evidence of efficacy for this treatment strategy but one RCT identified in the grey literature showed a 65% reduction in risk of IMV/death (p=0.02) and a marked, although not significant, reduction in risk of death with mavrilimumab versus placebo (p=0.07).[37] The search in the grey literature also provided information on another GM-CSF inhibitor, lenzilumab, which was used in addition to SOC in hypoxic hospitalised patients (receiving or not oxygen therapy) was superior to placebo +SOC in improving survival without ventilation. Of interest, patients with CRP <150 mg/L and age <85 years were those who had the greatest benefit from lenzilumab.[38] In addition, a press release reported on the GM-CSF inhibitor otilimab and the data of a preplanned analysis of the OSCAR trial.[39] Patients aged 70 and over receiving otilimab in addition to SOC had a higher probability of being alive and free of respiratory failure at day 28 compared with those in the same age range receiving placebo in addition to SOC. Furthermore, 60-day mortality was significantly lower in otilimab-treated patients aged 70 and over.

Type I interferons

Two small RCTs at high RoB did not observe any benefit after adding interferon beta to SOC.[40 41]

Convalescent plasma and non-SARS-CoV-2 immunoglobulins

Five RCTs (two at high and two at unclear RoB) were retrieved by the search update and one of them was underpowered.[42–45] None of the studies showed clear efficacy on mortality or other major clinical outcomes by adding convalescent plasma to SOC. One small RCT at high RoB on the use of non-SARS-CoV-2 immunoglobulins was also retrieved by the search update showed some benefit in reducing hospital or ICU stay.[46]

Anti-SARS CoV-2 monoclonal antibodies

The new SLR identified one RCT enrolling hospitalised patients with moderate-to-severe COVID-19 and assessing bamlavimab monotherapy.[47] The study failed to provide any benefit on clinical outcomes (eg, 90-day mortality).

RCT data in patients with mild COVID-19 (non-hospitalised or hospitalised without oxygen therapy)

Two RCTs assessing HCQ in patients with mild to moderate COVID-19 were retrieved(table 3). One was stopped for futility,[48] while the other one compared two therapeutic strategies: HCQ or favipiravir in a small sample of hospitalised patients (n=50 in each group) with mild to moderate disease not receiving oxygen supplementation, showing no efficacy on SARS-CoV-2 PCR negativity development or regression of abnormal radiography.[49] The latter article was retracted while preparing this manuscript.[50]

A large RCT at unclear RoB enrolling non-hospitalised patients with mild COVID-19 demonstrated weak improvement of the composite outcome death or hospitalisation with colchicine.[51]

Two small RCTs, one at high and one at unclear RoB, did not detect any differences following the administration of one dose of PEG-IFN lambda or placebo in non-hospitalised patients with mild COVID-19.[52 53]

Finally, the administration of one dose of PEG IFN-α2b instead of placebo in addition to SOC allowed a higher number of hospitalised patients with moderate COVID-19 to achieve clinical improvement on day 15.[54]

As far as mAb against the SARS-CoV-2 spike protein are concerned, the SLR identified three RCTs enrolling non-hospitalised patients with mild to moderate COVID-19.[55–57] The combination of bamlanivimab and etesevimab, as well as of casirivimab and imdevimab administrated within the first week after symptom onset was able to significantly reduce viral load. However, casirivimab and imdevimab were effective only in patients seronegative at baseline. Conversely, bamlanivimab monotherapy failed to significantly reduce viral load in non-hospitalised patients. In addition, the results of the antiviral arm of the RECOVERY trial, retrieved in the grey literature,[58] showed that casirivimab and imdevimab are also able to reduce 28-day mortality in seronegative patients (rate ratio=0.80, 95% CI 0.70 to 0.91, p=0.0010).

Data from observational studies and case reports

As summarised in online supplemental table 2 for several compounds, no RCTs were retrieved by the SLR update. Among these, two studies deserve to be commented being the only few of this kind available so far. Two retrospective trials at high of bias compared the efficacy of methylprednisolone (MTP ≥1 mg/kg/day)[54] or 250–500 mg for ≥3 days) versus dexamethasone (DEXA ≥6 mg for ≥7 days). Both studies showed a reduction of death in the group treated with MTP. For the study by Ko *et al*,[59] only the subgroup receiving IMV had a lower RR (0.480, 95% CI 0.235 to 0.956),[54] while in the study from Pinson *et al*,[60] the mortality

Table 3 Effect of immunomodulatory therapies in mild-to-moderate COVID-19. Results from randomized controlled trials.

Drug	Author (ref)	Intervention comparator(s)	Timepoint (days)	N treated	Results	RoB
Hydroxychloroquine	Dabbous *et al*[49]	HCQ Favipiravir	14	50 50	2 successive negative SARS-CoV-2 PCR tests 48 hours apart RR (95% CI) 1.17 (0.8 to 1.7) Radiological abnormalities RR (95% CI) 1.20 (0.6 to 2.5)	High
Colchicine	Tardif *et al*[51]	COL PBO	30	2235 2253	RR (95% CI) Death 0.56 (0.19 to 1.66) Hospitalisation 0.75 (0.57 to 0.99) IMV 0.50 (0.23 to 1.07)	Unclear
PEG-interferon alpha	Pardit *et al*[54]	PEG-IFN alpha +SOC SOC	15	20 20	Clinical improvement (WHO 7-point ordinal scale) p<0.05	High
PEG-interferon lambda	Jagannathan *et al*[52]	PEG-IFN lambda-1a PBO	28	60 60	Time to cessation of viral shedding p=0.29	Unclear
	Feld *et al*[53]	PEG-IFN lambda-1a PBO	7	30 30	Negative RT-PCR, RR (95% CI) 1.26 (0.9 to 1.7) Improvement of respiratory symptoms p=0.06	High

Results from randomised controlled trials.
COL, colchicine; HCQ, hydroxychloroquine; IMV, invasive mechanical ventilation; PBO, placebo; PEG-IFN, pegylated interferon; RoB, risk of bias; RR, relative risk; RT-PCR, real time PCR; SOC, standard of care.

and transfer to ICU were numerically lower, although no statistical tests were presented.

DISCUSSION

The update of the SLR demonstrated that although a higher number of RCTs is now available assessing new immunomodulatory compounds, a knowledge gap on some therapeutic strategies and on mild-to-moderate COVID-19 still exists and too many low quality/low level of evidence studies are being published. We therefore focused our attention on RCTs and not on observational studies that are still included in the SLR and reported for the sake of comprehensiveness but not discussed in detail in this manuscript.

The new RCTs demonstrated that tocilizumab and some JAK inhibitors, such as baricitinib and tofacitinib, are effective, particularly in association with GC. The role of tocilizumab was unclear based on the results gathered in the previous SLR since there was no strong positive signal in papers published in peer-reviewed journals while the largest positive study, the REMAP-CAP, had only been published as a preprint. The additional data from the tocilizumab arm of the RECOVERY trial, the post hoc analysis of the CORIMUNO-19 TOCI-1 and the meta-analysis of RCTs published in the JAMA helped clarifying the scenario. Likewise, anti-IL6 receptor antibodies have received a strong recommendation from WHO in patients with severe and critical COVID-19.[61]

As far as JAK inhibitors are concerned, the previous SLR included an article supporting the efficacy of baricitinib in combination with remdesivir and no evidence on tofacitinib was available. In this new SLR, the results from the COV-BARRIER trial with baricitinib and from an independent tofacitinib trial point to a possible JAK inhibition therapeutic application of these compounds, at least in some subgroups of patients (patients on oxygen, including high flow oxygen) but the grey literature pointed to non-efficacy of JAK-2 inhibition. Likewise, selected patients may benefit from other strategies such as convalescent plasma and anti-viral monoclonal antibodies that seem to find a role only in seronegative patients with early disease.

It is important to note that heterogeneity across studies, in terms of outcomes, timepoints and SOC protocols still remains, although to a lesser extent. In particular, after the publication of the results from the GC arm of the RECOVERY trial, GCs were implemented in most SOC protocols and this allowed to better understand the potential of combining them with anti-cytokine molecules in RCTs, although with the limitation of this not being a predefined study arm.

Furthermore, recently published studies may still include patient cohorts enrolled during the first wave and therefore with all the major pitfalls highlighted in our previous SLR.[1]

In conclusion, this SLR informed the EULAR initiative to update the points to consider on the use of immunomodulatory therapies in COVID-19.[62] Although better evidence is available compared with the previous SLR, the need for RCT with combination therapy (GC +anti-cytokines) versus monotherapy with GC still remains alongside the need for standardisation of inclusion

criteria and outcomes to ultimately improve the care and prognosis of affected people.

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