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CONCISE REPORT

2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19

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ABSTRACT

Objectives: To update the EULAR Points to consider (PtCs) on the use of immunomodulatory therapies in COVID-19.

Methods: According to the EULAR standardised operating procedures, a systematic literature review up to July 14, 2021 was conducted and followed by a consensus meeting of an international multidisciplinary Task Force. The new statements were consolidated by formal voting.

Results: We updated 2 overarching principles (OP) and 12 PtC. Evidence was only available in moderate to severe and critical patients. Glucocorticoids alone or in combination with tocilizumab are beneficial in COVID-19 cases requiring oxygen therapy and in critical COVID-19. Use of Janus kinase inhibitors (baricitinib and tofacitinib) is promising in the same populations of severe and critical COVID-19. Anti-SARS-CoV-2 monoclonal antibodies and convalescent plasma may find application in early phases of the disease and in selected subgroups of immunosuppressed patients. There was insufficient robust evidence for the efficacy of other immunomodulators with further work being needed in relation to biomarker-based stratification for IL-1 therapy

Conclusions:

Growing evidence supports incremental efficacy of glucocorticoids alone or combined with tocilizumab/Janus kinase inhibitors in moderate to severe and critical COVID-19. Ongoing studies may unmask the potential application of other therapeutic approaches. Involvement of Rheumatologists, as systemic inflammatory diseases experts, should be encouraged in clinical trials of immunomodulatory therapy in COVID-19.

KEYWORDS SARS-CoV-2, COVID-19, immunomodulatory therapy, glucocorticoids pathophysiology.

KEY MESSAGES

What is already known about this subject?

- Results from the previous systematic literature review highlighted that glucocorticoids, mainly dexamethasone, is the only drug with proven efficacy in reducing COVID-19 mortality in patients requiring oxygen therapy and in critically ill patients.
- Other Immunomodulatory treatments used in rheumatology may be beneficial in selected subgroups of patients with COVID-19 and in specific phases of the disease.

What does this study add?

- We updated the existing EULAR Points to Consider (PtC) on immunomodulatory therapies in COVID-19 in light of the most recent literature available.
- Tocilizumab in combination with glucocorticoids is beneficial in COVID-19 cases requiring oxygen therapy and in critical COVID-19. Use of Janus kinase inhibitors (baricitinib and tofacitinib) is promising in the same populations.
- Anti-SARS-CoV-2 monoclonal antibodies and convalescent plasma may find application in early phases of the disease and in selected subgroups of immunosuppressed patients.
- Other immunomodulators failed to consistently demonstrate efficacy on mortality and other clinical outcomes at any disease stage or confirmatory evidence for biomarker-based stratification is currently lacking.

How might this impact on clinical practice?

- We propose for healthcare providers the most up-to-date treatment strategies of using immunomodulators in the treatment of moderate-to-severe and critical COVID-19.
- The updated PtCs open the way to a new paradigm: the treatment of severe and critical acute infections may benefit from immunomodulatory treatments usually reserved for autoimmune and inflammatory diseases.

INTRODUCTION

The use of immunomodulatory therapies in SARS-CoV-2 infection is a rapidly evolving field and it represents a challenge for the scientific community. New evidence informing best practice for clinical management of patients infected with SARS-CoV-2 and presenting COVID-19 are released on a weekly basis, leading to the continuous need for updated policies in the field. In this context, several scientific societies, including EULAR have formulated guidance on treatment of COVID-19.[1-3] In order to propose the most up-to-date treatment strategies to physicians and patients, efforts to update these recommendations in a timely manner must be undertaken. The aim of this project was to update the EULAR Points to Consider (PtC) on the use of immunomodulatory therapies in COVID-19 from the rheumatology perspective through a systematic literature review (SLR)-based approach.

METHODS

The multidisciplinary task force (TF) that developed the first version of the PtC guided by the 2014 updated EULAR standardised operating procedures.[4] reconvened in a virtual meeting on June 30, 2021. Two fellow clinicians (AA and AN), guided by the methodologist (PMM), performed an update of the systematic literature review (SLR) retrieving individual studies on the management of SARS-CoV-2 infection with immunomodulatory therapies published between December 11, 2020 and June 30, 2021 (subsequently up-dated up to July 14, 2021) (Online Supplementary text 1). In addition, a search to retrieve individual studies on the management of SARS-CoV-2 infection with anti-SARS-CoV-2 monoclonal antibodies was performed (Online Supplementary text 2). The SLR is published separately, however, it forms an integral part of the project. Grey literature, namely randomized controlled trials (RCTs) published as full online non-peer-reviewed pre-prints or in part as press releases, was also included for the sake of completeness but did not inform the PtC.

Statements updated by the steering group were presented to the TF, and discussed against the existing ones, based on the SLR results. The statements were accepted if more than 75% of the task force approved the wording in the first round (informal voting), 67% in the second voting round and more

than 50% in the third round. The level of evidence (LoE) supporting each statement was assigned. Finally, task force members anonymously indicated their level of agreement (LoA) with each PtC online (numerical rating scale ranging from 0='completely disagree' to 10='completely agree').

RESULTS

The updated PtC are shown in Table 1, and the modifications compared with the previous ones are shown in Table 2.

The PtC are intended to provide guidance on therapeutic aspects, and the target users are health care providers involved in the care of patients infected with SARS-CoV-2 infection, patients and policy makers.

Overarching principles

The overarching principles remained unchanged compared to the 2020 version. More than a year after the start of the pandemic, the heterogeneity of SARS-CoV-2 infection clinical picture, reflecting different pathogenic mechanisms, is widely recognized.[5] Patients infected by SARS-CoV-2 may experience a set of manifestations ranging from asymptomatic infection, mild disease to severe disease with acute respiratory distress syndrome (ARDS), multi-organ failure and death. In this regard, response to immunomodulatory therapy varies according to disease stage, with the best efficacy of these compounds observed in severe but not critical disease (Table 1).

Points to consider

Since the formulation of the original set of PtCs, over 300 articles with various level of evidence (LoE) investigating immunomodulatory agents in SARS-CoV-2 infection were published.[6] Besides studies with drugs already mentioned in the previous PtCs, such as tocilizumab (TCZ) or anakinra, studies with new drugs including sarilumab, tofacitinib (TOFA), baricitinib, and colchicine, among others, were available, either as monotherapy or in combination treatment with glucocorticoids (GC).

On this basis, the Steering Group agreed to keep PtC-1 and PtC-2 unchanged since they remain valid statements supported by current evidence and formulate new statements based on the recent evidence (or lack thereof) for individual classes of compounds, whenever possible, or single drugs (Tables 1 and 2).

PtC-1) In non-hospitalised patients with SARS-CoV-2 infection there is currently no evidence to support the initiation of immunomodulatory therapy (LoE 2/3/4).

PtC-2) In hospitalised patients with SARS-CoV-2 infection that do not need oxygen therapy there is currently no evidence to support the initiation of immunomodulatory therapy to treat their COVID-19 (LoE 2/3/4).

The group agreed to keep PtC-1 and PtC2 unchanged since they remain valid statements supported by current evidence.

PtC-3) Hydroxychloroquine should be avoided for treating any stage of SARS-CoV-2 infection since it does not provide any additional benefit to the standard of care, and could worsen the prognosis in more severe patients particularly if co-prescribed with azithromycin (LoE 2).

The group agreed to keep this PtC unchanged since further evidence against the use of hydroxychloroquine has emerged.[7-14]

PtC-4) In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation, systemic glucocorticoids should be used since they can decrease mortality; most evidence concerns the use of dexamethasone (LoE 2/3).

As PtC-1, the group agreed to keep this PtC unchanged but in this case on the basis of lack of new evidence. In fact, the 3 new RCTs gathered by the SLR update were underpowered, thereby providing unreliable results and therefore could not be used to formulate the PtC. One retrospective trial comparing the efficacy of methyprednisolone (MTP ≥ 1mg/kg/d for ≥ 3d) versus dexamethasone

(DEXA ≥ 6mg for ≥7d) showed a reduction of mortality in the group of patients receiving MV treated with MTP (Relative risk (RR) 0.48 (95% confidence interval (CI) 0.23-0.96). However, the small number of patients, retrospective design and high risk of bias for this study did not allow definitive conclusions regarding superiority of any compound and could therefore not inform the PtCs.[15]

PtC-5) In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation combination of glucocorticoids and tocilizumab should be considered since it reduces disease progression and mortality (LoE 2). More data are needed to fully appreciate the effect of other IL-6R inhibitors (LoE 2/3).

This PtC was modified encompassing not only TCZ but the entire class of IL-6R inhibitors. Four new RCTs pertained to TCZ [16-19] alongside the 90 days post-hoc analysis of the CORIMUNO-19 TOCI trial.[20] Among these, RECOVERY, REMAP-CAP and the post -hoc analysis of CORIMUNO-19 TOCI (the latter in the subgroup of patients with C reactive protein (CRP) >15.0 mg/dL) showed reduction of death at Day 21 (RR 0.27, 95% CI 0.12-0.72), day 28 (RR 0.82, 95% CI 0.75-0.90), and Day 90 respectively (RR 0.79, 95% CI 0.63-0.97) respectively. In addition, a reduction of progression to invasive mechanical ventilation (IMV) or death at day 21 [19] or day 90 [20] or an increase in cardiovascular or respiratory support-free days [18] was observed. Of note, the proportion of patients receiving GC as part of the standard of care (SOC) was very heterogeneous among trials, with a difference observed between trials starting before and after the positive results of the GC arm of the RECOVERY trial. It is noteworthy that in contrast to 2 positive RCTs where a high percentage of patients were receiving concomitant GC (82% to 93%),[18,19] only up to 50% of patients were receiving concomitant GC in the COVACTA trial, which failed to show efficacy in reducing death or improving clinical status.[16] In addition, a recent meta-analysis of RCTs published in JAMA confirmed the efficacy of TCZ on all-cause mortality (odds ratio (OR) 0.83, 95% CI 0.72-0.94) and progression to IMV, ExtraCorporeal Membrane Oxygenation (ECMO) or death (OR 0.74, 95%CI 0.66-0.82) at day 28.[21] It is important to mention that the survival benefit at 28 days was essentially

observed only in patients also on glucocorticoids. Furthermore, the statistically significant benefit in survival at 90 days is the most relevant finding. Of note, much of what drove the statistical significance for improved mortality were the non-blinded larger randomized trials.

The evidence regarding sarilumab (SARI) is scarcer although encouraging, with a small arm in REMAP-CAP trial (n=44 patients) showing a reduction in death and cardiovascular/respiratory organ-support free days [18] while another RCT comparing 200mg or 400mg of SARI and placebo showed no efficacy on death, progression to IMV or admission to intensive care unit (ICU).[22] Of interest, in a metanalysis of IL-6R inhibitors, in the subgroup of patients receiving GC compared to those who did not, mortality at day 28 was significantly reduced only in the GC group for TCZ (ratio of OR (ROR) 0.69, 95% CI 0.52-0.91 p=0.008), with only a non-significant trend for SARI (ROR 0.77, 95% CI 0.64-1.31 p=0.34).

PtC-6) In COVID-19 there is no robust evidence to support the use of anakinra and canakinumab at any disease stage (LoE 2).

The only RCT available in the 2020 version of the PtC on anakinra used at a high dose of 400mg/day for 3 to 6 days (CORIMUNO-19 ANA) was negative in patients with mild-to-moderate COVID-19 pneumonia requiring at least 3L/min oxygen but not receiving non-invasive ventilation (NIV) or IMV at randomization.[23] In addition, one RCT looking into a specific group of COVID-19 patients, namely those with elevated soluble urokinase plasminogen activator (suPAR) equal to or above 6 ng/ml which is considered as a predictor of unfavorable outcome. In this population, anakinra 100mg subcutaneously for 7 to 10 days increased number of patients improving WHO CPS at day 28 (0.36 (95% CI 0.26-0.50) and decreased mortality at day 28: 3.2% vs 6.9% (HR=0.45, p=0.045).[24] Further studies are necessary to address the validity of this biomarker for predicting a possible effect of anakinra in this subgroup of patients. With regard to canakinumab, a 2020 press-release RCT indicated that it did not meet its primary and secondary endpoints.[25] Large trials recruiting severe cases of COVID-19 are warranted.

PtC-7) In COVID-19 there is no robust evidence to support the use of low-dose colchicine at any disease stage (LoE 2).

Compared to 2020, the new SLR updated gathered 2 additional RCTs, a large study enrolling almost 5000 non-hospitalized patients with mild disease [26] and a small study including 72 hospitalized patients, most of whom required oxygen therapy.[27] The results of both studies were not rated solid enough to recommend in favor of colchicine. Moreover, both studies used a rather low dose, hence the group deemed appropriate to specify this in the PtC since it was not possible to rule out whether higher doses might be beneficial. In addition, a press release reported that the colchicine arm of the RECOVERY trial, enrolling hospitalized patients with COVID-19, has closed due to lack of evidence that further recruitment will prove a reduction of mortality. The interim results have been published as preprint.[28]

PtC-8) In patients with COVID-19 requiring oxygen therapy, non-invasive ventilation or high-flow oxygen, the combination of glucocorticoids and baricitinib or tofacitinib could be considered since it might decrease disease progression and mortality (LoE 2).

The only RCT available on baricitinib (BARI) in SARS-CoV-2 infection included in the 2020 version [29] and compared remdesevir+BARI versus remdesevir+placebo. In addition, The Fourth iteration of the Adaptive COVID-19 Treatment Trial (ACTT-4), although published in the grey literature and therefore not used to inform the PtCs; compared BARI+remdesivir+placebo versus remdesivir+DEXA+placebo and met pre-defined futility criteria in an interim analysis thereby closed enrollment in April 2021 according to a press release.[30] In a new study (COV-BARRIER trial), BARI in addition to SOC (80% participants receiving GC (92% DEXA)) showed no significant efficacy in reducing progression to the composite primary endpoint defined by the proportion who progressed to high-flow oxygen, NIV/IMV or death by day 28. However, the all-cause 28-day mortality in the BARI group was decreased from 13% to 8% (HR=0·57 [95% CI 0·41–0·78]; p=0·0018) and at day 60: 10% vs 15% (HR=0·62 [95% CI 0·47–0·83]; p=0·005).[31]

One new RCT [32] comparing TOFA+SOC (n=144) to placebo+SOC (n=144) reported a significant improvement of the composite outcome of respiratory failure or mortality at day 28 (RR 0.63, 95% CI 0.41-0.97) vs placebo+SOC in a population where 90% of patients were receiving GC as part of SOC. No new evidence other than the previously published negative RCT on ruxolitinib was retrieved.

PtC-9) An evolving RCT landscape cannot yet allow formal recommendation of the use of GM-CSF inhibitors (mavrilimumab, otilimab, lenzilumab) in COVID-19 (LoE 2)

The 2020 SLR gathered only a few studies with low level of evidence on GM-CSF inhibitors. Although the SLR update identified only 1 RCT on mavrilimumab, the group discussed the large proportion of ongoing RCTs, not only on mavrilimumab but also on other GM-CSF inhibitors (otilimab, lenzilumab), available in the grey literature (both as press releases and as preprints). On this basis, they deemed appropriate to formulate a PtC conveying the message that the current lack of evidence to recommend either in favor or against is accompanied by an evolving body of evidence that will soon be available in peer reviewed journals.

PtC-10) In patients without hypogammaglobulinemia and with symptom onset > 5 days there is robust evidence against the use of convalescent plasma (LoE 2)

Among the RCTs published on convalescent plasma (CP) (n=7) 4 were retrieved by the SLR update. Of interest, a distinction was drawn by the TF based on the timing of CP administration (i.e. before or after day 5 of symptom onset). In fact, a large RCT including more than 5000 patients in each treatment arm (CP+SOC vs placebo+ SOC), CP was not effective in reducing the composite outcome of progression to IMV or death at day 28 (RR 0.99, 95%CI 0.93–1.05 p=0.79) when administered after this timeframe.[33] It is important to clarify that this PtC was informed by robust data against CP showing benefit while no evidence about CP being harmful was retrieved by SLR.

PtC-11) In patients at risk of severe COVID-19 course, with symptom onset <5 days or still seronegative, monoclonal antibodies against SARS-CoV-2 spike protein should be considered (LoE 2)

The new SLR conducted to gather studies on monoclonal antibodies against SARS-CoV-2 spike protein, retrieved 4 RCTs, three of which enrolled non-hospitalized patients with mild to moderate COVID-19 [34-36] and one enrolling hospitalized patients with moderate-to-severe COVID-19.[37] The combination of bamlanivimab and etesevimab as well as of casirivimab and imdevimab administrated within the first week after symptom onset were able to significantly reduce viral load. However, casirivimab and imdevimab were effective only in patients seronegative at baseline.

Conversely, bamlanivimab monotherapy not only failed to significantly reduce viral load in non-hospitalised patients, but also failed to provide any benefit on clinical outcomes (e.g. 90 days mortality) in hospitalised patients.[37] It is important to mention that the specific monoclonal antibodies have different activities against variants, so in addition to the above-mentioned data, regional prevalence of variants must be taken into account when selecting a particular product.

PtC-12) In patients with COVID-19 there is currently insufficient evidence to recommend the use of other immunomodulatory drugs, including interferon alpha, interferon beta, interferon kappa, interferon lambda, leflunomide, non-SARS CoV-2 IVIg (LoE 2), eculizumab and cyclosporine (LoE 3).

Interferon lambda has been added since no RCT was available in the previous SLR and the 2 RCTs retrieved by the SLR update were not solid enough to formulate a new PtC. A change of LoE was done for interferon alpha since a small RCT was retrieved by the search update.[38]. The group did not comment on drugs for which published literature was of LoE<3.

DISCUSSION

Since the release of the first EULAR-endorsed PtCs on immunomodulatory therapy of SARS-CoV-2 infection, new evidence has accumulated on the efficacy and safety of various compound with most evidence pertaining to moderate to severe/critical COVID-19. The aim of this update was to provide clinicians involved in the care of people with SARS-CoV-2 infection with an update on the use of immunomodulatory therapies in COVID-19, based on available literature and as seen from the rheumatology perspective.

All the statements are based on a thorough SLR and on conclusions of an international rheumatology/multidisciplinary team. All studies, albeit RCTs, were highly heterogeneous and at high or unclear risk of bias, hence the experts' opinion was instrumental to reach consensus on if and how to update the existing statements.

Until now, only 3 drugs have been recommended by WHO for COVID-19, DEXA and TCZ for patients requiring oxygen therapy and critical patients and the combination of casirivimab and imdevimab for early patients at risk of severe form and not vaccinated or having not responded to vaccination.[2]

Besides the 3 statements on HCQ, GCs and anakinra, the group developed several new PtCs and modified the existing ones since more evidence about numerous drugs has accrued (Table 2). Moreover, the discontinuation of some RCTs for futility and the availability of interim data of some successful RCTs from the grey literature, clarified the role of some immunomodulatory compounds in the scenario of the pandemic although these could not be used to formulate recommendations in favor or against.

In particular, it was possible to formulate statements in favor of TCZ in combination with GCs and against convalescent plasma, except in specific in subgroups of patients based on a consistent number of peer-reviewed RCTs. Based on the evidence on convalescent plasma and monoclonal antibodies against SARS-CoV-2 spike protein, it is tempting to speculate that a polyclonal response may be better to activate effector functions than a monoclonal response.

Data on JAK inhibitors are promising in some subgroups. Lastly, the use of colchicine and GM-CSF inhibitors is pending the release of more solid evidence.

In conclusion, the update of these EULAR PtCs provide relevant and updated guidance on immunomodulatory therapy utilization from the rheumatology perspective and opens the way to a new paradigm: the treatment of immunopathology associated with severe and critical acute infections may benefit from immunomodulatory treatments usually given for autoimmune and inflammatory diseases.

Table 1. Overarching principles and points to consider on the use of immunomodulatory treatment in COVID-19, with levels of evidence (LoE) and levels of agreement (LoA).

Overarching principles	**LoA mean (SD); % of votes ≥8/10**
A. The phenotype of SARS-CoV-2 infection is heterogeneous ranging from asymptomatic to lethal disease due to multi-organ damage.	9.92 (0.3); 100%
B. SARS-CoV-2 infection may need different treatment approaches, including anti-viral, oxygen therapy, anti-coagulation and/or immunomodulatory treatment at different stages of the disease.	9.92 (0.3); 100%
Points to consider	
1. In non-hospitalised patients with SARS-CoV-2 infection there is currently no evidence to support the initiation of immunomodulatory therapy (LoE 2/3/4).	9.58 (1.0); 96%
2. In hospitalised patients with SARS-CoV-2 infection that do not need oxygen therapy there is currently no evidence to support the initiation of immunomodulatory therapy to treat their COVID-19 (LoE 2/3/4).	9.04 (1.6); 88%
3. Hydroxychloroquine should be avoided for treating any stage of SARS-CoV-2 infection since it does not provide any additional benefit to the standard of care, and could worsen the prognosis in more severe patients particularly if co-prescribed with azithromycin (LoE 2).	9.92 (0.3) 100%
4. In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation, systemic glucocorticoids should be used since they can decrease mortality; most evidence concerns the use of dexamethasone (LoE 2/3).	9.75 (0.4) 100%
5. In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation combination of glucocorticoids and tocilizumab should be considered since it reduces disease progression and mortality (LoE 2). More data are needed to fully appreciate the effect of other IL-6R inhibitors (LoE 2/3).	9.17 (1.7) 87.5%
6. In COVID-19 there is no robust evidence to support the use of anakinra or canakinumab at any disease stage (LoE 2).	9.16 (0.9) 96%
7. In COVID-19 there is no robust evidence to support the use of low-dose colchicine at any disease stage (LoE 2)	9.5 (0.9) 96%
8. In patients with COVID-19 requiring oxygen therapy, non-invasive ventilation or high-flow oxygen, the combination of glucocorticoids and baricitinib or tofacitinib could be considered since it might decrease disease progression and mortality (LoE 2).	8.92 (1.4) 87.5%
9. An evolving RCT landscape cannot yet allow formal recommendation of the use of GM-CSF inhibitors (mavrilimumab, otilimab, lenzilumab) in COVID-19 (LoE 2)	9.13 (0.9) 92%
10. In patients without hypogammaglobulinemia and with symptom onset > 5 days there is robust evidence against the use of convalescent plasma (LoE 2)	9.04 (1.9) 83.3

11. In patients at risk of severe COVID-19 course, symptom onset <5 days or still seronegative, monoclonal antibodies against SARS-CoV-2 spike protein should be considered (LoE 2)	9.29 (1.1) 92%
12. In COVID-19 there is currently insufficient evidence to recommend the use of other immunomodulators, including interferon kappa, interferon beta, interferon lambda, leflunomide, non-SARS CoV-2 IVIg (LoE 2), eculizumab, cyclosporine, interferon alpha (LoE 3)	9.79 (0.4) 100%
SD, standard deviation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019	

Table 2 Comparison of the 2020 and 2021 points to consider on the use of immunomodulatory treatment in SARS-CoV-2 infection

2021 (current) version	Changes performed	2020 version
Overarching principles		
A. The phenotype of SARS-CoV-2 infection is heterogeneous ranging from asymptomatic to lethal disease due to multi-organ damage.	Unchanged	A. The phenotype of SARS-CoV-2 infection is heterogeneous ranging from asymptomatic to lethal disease due to multi-organ damage.
B. SARS-CoV-2 infection may need different treatment approaches, including anti-viral, oxygen therapy, anti-coagulation and/or immunomodulatory treatment at different stages of the disease.	Unchanged	B. SARS-CoV-2 infection may need different treatment approaches, including anti-viral, oxygen therapy, anti-coagulation and/or immunomodulatory treatment at different stages of the disease.
Points to consider		
In non-hospitalised patients with SARS-CoV-2 infection there is currently no evidence to support the initiation of immunomodulatory therapy (LoE 2/3/4).	Unchanged	In non-hospitalised patients with SARS-CoV-2 infection there is currently no evidence to support the initiation of immunomodulatory therapy (LoE 2/3/4).
In hospitalised patients with SARS-CoV-2 infection that do not need oxygen therapy there is currently no evidence to support the initiation of immunomodulatory therapy to treat their COVID-19 (LoE 2/3/4).	Unchanged	In hospitalised patients with SARS-CoV-2 infection that do not need oxygen therapy there is currently no evidence to support the initiation of immunomodulatory therapy to treat their COVID-19 (LoE 2/3/4).
Hydroxychloroquine should be avoided for treating any stage of SARS-CoV-2 infection since it does not provide any additional benefit to the standard of care, and could worsen the prognosis in more severe patients particularly if co-prescribed with azithromycin (LoE 2).	Unchanged	Hydroxychloroquine should be avoided for treating any stage of SARS-CoV-2 infection since it does not provide any additional benefit to the standard of care, and could worsen the prognosis in more severe patients particularly if co-prescribed with azithromycin (LoE 2).
In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation, systemic glucocorticoids should be used since they can	Unchanged	In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation, systemic glucocorticoids should be used since they can decrease mortality; most

decrease mortality; most evidence concerns the use of dexamethasone (LoE 2/3).		evidence concerns the use of dexamethasone (LoE 2/3).
In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation combination of glucocorticoids and tocilizumab should be considered since it reduces disease progression and mortality (LoE 2). More data are needed to fully appreciate the effect of other IL-6R inhibitors (LoE 2/3).	Modified	An evolving RCT landscape cannot yet allow formal recommendation of the routine use of tocilizumab in patients with COVID-19 requiring oxygen therapy, non-invasive or invasive ventilation (LoE 2).
In COVID-19 there is no robust evidence to support the use of anakinra at any disease stage (LoE 2/4).	Modifies	In COVID-19 there is no robust evidence to support the use of anakinra or canakinumab at any disease stage (LoE 2).
In COVID-19 there is no robust evidence to support the use of low-dose colchicine at any disease stage (LoE 2)	New	Not applicable
In patients with COVID-19 requiring oxygen therapy, non-invasive ventilation or high-flow oxygen, the combination of glucocorticoids and baricitinib or tofacitinib could be considered since it might decrease disease progression and mortality (LoE 2).	Modified	In patients with COVID-19 requiring non-invasive ventilation or high-flow oxygen, the combination of remdesivir plus baricitinib could be considered since it can decrease time to recovery and accelerate improvement in clinical status (LoE 2).
An evolving RCT landscape cannot yet allow formal recommendation of the use of GM-CSF inhibitors (mavrilimumab, otilimab, lenzilumab) in COVID-19 (LoE 2)	New	Not applicable
In patients without hypogammaglobulinemia and with symptom onset > 5 days there is robust evidence against the use of convalescent plasma (LoE 2)	New	Not applicable
In patients at risk of severe COVID-19 course, symptom onset <5 days or still seronegative, monoclonal antibodies against anti-spike protein should be considered (LoE 2)	New	Not applicable
In COVID-19 there is currently insufficient evidence to recommend the use of other immunomodulators, including interferon kappa, interferon beta, interferon lambda, leflunomide, non-SARS CoV-2 IVIg (LoE 2), eculizumab, cyclosporine, interferon alpha (LoE 3)	Modified	In COVID-19 there is currently insufficient evidence to recommend the use of other immunomodulators, including ruxolitinib, IVIg, convalescent plasma therapy except in Ig-deficient patients, interferon kappa, interferon beta, leflunomide, colchicine (LoE 2), sarilumab, lenzilumab, eculizumab, cyclosporine, interferon alpha (LoE 3), canakinumab (LoE 4).
LoE, lovel of evidence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019		

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