CLINICAL SCIENCE

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

Alessia Alunno ,[1] Aurélie Najm ,[2] Pedro M Machado ,[3,4,5] Heidi Bertheussen,[6] Gerd-Rüdiger R Burmester ,[7] Francesco Carubbi ,[1] Gabriele De Marco,[8] Roberto Giacomelli,[9] Olivier Hermine,[10,11] John D Isaacs ,[12] Isabelle Koné-Paut ,[13,14] César Magro-Checa,[15] Iain B McInnes,[2] Pier Luigi Meroni ,[16] Luca Quartuccio ,[17] A V Ramanan,[18,19] Manuel Ramos-Casals,[20] Javier Rodríguez Carrio,[21] Hendrik Schulze-Koops ,[22] Tanja A Stamm ,[23] Sander W Tas,[24] Benjamin Terrier ,[25] Dennis G McGonagle,[8] Xavier Mariette [26,27]

**Handling editor** David S Pisetsky

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-221366).

For numbered affiliations see end of article.

**Correspondence to**
Professor Xavier Mariette, Department of Rheumatology, INSERM UMR1184, Le Kremlin Bicêtre, France;
xavier.mariette@aphp.fr

AA and AN are joint first authors.
DGM and XM are joint senior authors.

Received 16 August 2021
Accepted 29 September 2021



**To cite:** Alunno A, Najm A, Machado PM, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-221366

## 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 14 July 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 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.

## 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.

## 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.

## Key messages

**How might this impact on clinical practice or future developments?**

- 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.

## 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 30 June 2021. Two fellow clinicians (AA and AN), guided by the methodologist (PMM), performed an update of the SLR retrieving individual studies on the management of SARS-CoV-2 infection with immunomodulatory therapies published between 11 December 2020 and 30 June 2021 (subsequently updated up to 14 July 2021) (online supplemental 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 supplemental text 2). The SLR is published separately, however, it forms an integral part of the project. Grey literature, namely randomised controlled trials (RCTs) published as full online non-peer-reviewed preprints 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 TF 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, TF members anonymously indicated their level of agreement with each PtC online (numerical rating scale ranging from 0='completely disagree' to 10='completely agree').

## RESULTS

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

The PtCs are intended to provide guidance on therapeutic aspects, and the target users are healthcare 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 with the 2020 version. More than a year after the start of the

**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)

| | LoA mean (SD); % of votes ≥8/10 |
|---|---|
| Overarching principles | |
| The phenotype of SARS-CoV-2 infection is heterogeneous ranging from asymptomatic to lethal disease due to multiorgan damage. | 9.92 (0.3); 100 |
| SARS-CoV-2 infection may need different treatment approaches, including antiviral, oxygen therapy, anticoagulation and/or immunomodulatory treatment at different stages of the disease. | 9.92 (0.3); 100 |
| 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). | 9.58 (1.0); 96 |
| 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 |
| 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 coprescribed with azithromycin (LoE 2). | 9.92 (0.3) 100 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| In patients without hypogammaglobulinaemia and with symptom onset >5 days there is robust evidence against the use of convalescent plasma (LoE 2) | 9.04 (1.9) 83.3 |
| 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 |
| 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) | 9.79 (0.4) 100 |

GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IL-6R, Interleukin-6 receptor; RCT, randomised controlled trial.

**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 (previous) version |
|---|---|---|
| Overarching principles | | |
| The phenotype of SARS-CoV-2 infection is heterogeneous ranging from asymptomatic to lethal disease due to multiorgan damage. | Unchanged | The phenotype of SARS-CoV-2 infection is heterogeneous ranging from asymptomatic to lethal disease due to multiorgan damage. |
| SARS-CoV-2 infection may need different treatment approaches, including antiviral, oxygen therapy, anticoagulation and/or immunomodulatory treatment at different stages of the disease. | Unchanged | SARS-CoV-2 infection may need different treatment approaches, including antiviral, oxygen therapy, anticoagulation 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 coprescribed 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 coprescribed 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 decrease mortality; most evidence concerns the use of dexamethasone (LoE 2/3). | 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 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 hypogammaglobulinaemia 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 antispike protein should be considered (LoE 2) | New | Not applicable |
| 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) | Modified | In COVID-19 there is currently insufficient evidence to recommend the use of other immunomodulators, including ruxolitinib, intravenous immunoglobin, 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). |

GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IL-6R, Interleukin-6 receptor; LoE, lovel of evidence; ; RCT, randomised controlled trial.

pandemic, the heterogeneity of SARS-CoV-2 infection clinical picture, reflecting different pathogenic mechanisms, is widely recognised.[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, multiorgan 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 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 (BARI) 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 PtC-2 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 coprescribed 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 GC should be used since they can decrease mortality; most evidence concerns the use of dexamethasone (DEXA) (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 three 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 ≥1 mg/kg/days for ≥3 days) vs DEXA (DEXA ≥6 mg for ≥7 days) showed a reduction of mortality in the group of patients receiving MV treated with MTP (relative risk (RR) 0.48 (95% CI 0.23 to 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 GC and TCZ 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 >15.0 mg/dL) showed reduction of death at day 21 (RR 0.27, 95% CI 0.12 to 0.72), day 28 (RR 0.82, 95% CI 0.75 to 0.90) and day 90 respectively (RR 0.79, 95% CI 0.63 to 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 two positive RCTs where a high percentage of patients were receiving concomitant GC (82%–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 (OR 0.83, 95% CI 0.72 to 0.94) and progression to IMV, extracorporeal membrane oxygenation or death (OR 0.74, 95% CI 0.66 to 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 GC. 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 randomised 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 200 mg or 400 mg of SARI and placebo showed no efficacy on death, progression to IMV or admission to intensive care unit.[22] Of interest, in a meta-analysis of IL-6R inhibitors, in the subgroup of patients receiving GC compared with 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 to 0.91 p=0.008), with only a non-significant trend for SARI (ROR 0.77, 95% CI 0.64 to 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 400 mg/day for 3 to 6 days (CORIMUNO-19 ANA) was negative in patients with mild-to-moderate COVID-19 pneumonia requiring at least 3 L/min oxygen but not receiving non-invasive ventilation (NIV) or IMV at randomisation.[23] In addition, one RCT looking into a specific group of COVID-19 patients, namely those with elevated soluble urokinase plasminogen activator equal to or above 6 ng/mL which is considered as a predictor of unfavourable outcome. In this population, anakinra 100 mg subcutaneously for 7–10 days increased number of patients improving WHO CPS at day 28 (0.36 (95% CI 0.26 to 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 two additional RCTs, a large study enrolling almost 5000 non-hospitalised patients with mild disease[26] and a small study including 72 hospitalised patients, most of whom required oxygen therapy.[27] The results of both studies were not rated solid enough to recommend in favour 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 hospitalised 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, NIV or high-flow oxygen, the combination of GC and BARI or TOFA could be considered since it might decrease disease progression and mortality (LoE 2).

The only RCT available on 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-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 predefined 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 to 0.78); p=0.0018) and at day 60: 10% vs 15% (HR=0.62 (95% CI 0.47 to 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 to 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 LoE on GM-CSF inhibitors. Although the SLR update identified only one 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 favour or against is accompanied by an evolving body of evidence that will soon be available in peer-reviewed journals.

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

Among the RCTs published on CP (n=7), four were retrieved by the SLR update. Of interest, a distinction was drawn by the TF based on the timing of CP administration (ie, 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 to 1.05 p=0.79) when administered after this time frame.[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 four RCTs, three of which enrolled non-hospitalised patients with mild to moderate COVID-19[34–36] and one enrolling hospitalised 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 failed to significantly reduce viral load in non-hospitalised patients, and failed to provide any benefit on clinical outcomes (eg, 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 two 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, although 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 three 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 three 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 favour or against.

In particular, it was possible to formulate statements in favour of TCZ in combination with GCs and against CP, except in specific in subgroups of patients based on a consistent number of peer-reviewed RCTs. Based on the evidence on CP 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 Janus kinase 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 utilisation 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.

**Author affiliations**
[1]Internal Medicine and Nephrology Unit, Department of Life, Health & Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[2]Institute of Infection, Immunity and Inflammation, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
[3]Centre for Rheumatology and Department of Neuromuscular Diseases, University College London, London, UK
[4]National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC), University College London Hospitals NHS Foundation Trust, London, UK
[5]Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK
[6]Patient Research Partner, EULAR, Oslo, Norway

[7]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Freie Universität und Humboldt-Universität Berlin, Berlin, Germany
[8]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & The NIHR Leeds Biomedical Research Centre, Chapel Allerton Hospital, Leeds, UK
[9]Rheumatology and Clinical Immunology Unit, University of Rome "Campus Biomedico" School of Medicine, Rome, Italy
[10]Department of Hematology, Hôpital Necker, Assistance Publique - Hôpitaux de Paris, Paris, France
[11]Institut Imagine, Université de Paris, INSERM UMR1183, Paris, France
[12]Translational and Clinical Research Institute, Newcastle University and Musculoskeletal Unit, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[13]Department of Paediatric Rheumatology, Reference Centre for Autoinflammatory Diseases and Amyloidosis (CEREMAIA), Bicêtre University Hospital, AP-HP, Le Kremlin-Bicetre, France
[14]University of Paris Sud Saclay, Paris, France
[15]Department of Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, Netherlands
[16]Experimental Laboratory of Immunological and Rheumatologic Researches, Istituto Auxologico Italiano IRCCS, Milano, Italy
[17]Department of Medicine, Rheumatology Clinic, University of Udine, ASUFC Udine, Udine, Italy
[18]University Hospitals Bristol NHS Foundations Trust, Bristol, UK
[19]Translational Health Sciences, University of Bristol, Bristol, UK
[20]Department of Autoimmune Diseases, ICMiD, Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Department of Autoimmune Diseases, ICMiD, University of Barcelona, Hospital Clínic, Barcelona, Spain
[21]Department of Functional Biology, Immunology Area, Faculty of Medicine, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), University of Oviedo, Oviedo, Spain
[22]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, Ludwig-Maximilians University Munich, Munich, Germany
[23]Section for Outcomes Research, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna and Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Wien, Austria
[24]Department of Rheumatology and Clinical Immunology, Amsterdam Rheumatology and immunology Center, Amsterdam University Medical Centres, AMC/University of Amsterdam, Amsterdam, Netherlands
[25]Department of Internal Medicine, Cochin University Hospital, Paris, France; National Referral Centre for Systemic and Autoimmune Diseases, University Paris Descartes, Sorbonne Paris Cité, Paris, France
[26]Department of Rheumatology, INSERM UMR1184, Le Kremlin Bicêtre, France
[27]Department of Rheumatology, Université Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, INSERM UMR1184, Le Kremlin Bicêtre, France

**Twitter** Pedro M Machado @pedrommcmachado and John D Isaacs @ProfJohnIsaacs

**Contributors** All authors contributed and finally approved the current manuscript. AA and AN share first Authorship. DGM and XM share last Authorship.

**Funding** This work was funded by European Alliance of Associations in Rheumatology (EULAR) (CLI122). PMM is supported by the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the (UK) National Health Service, NIHR or the Department of Health. JDI is a NIHR Senior Investigator and his work is supported by the NIHR Newcastle Biomedical Research Centre in Ageing and Long-Term Conditions, and the Research Into Inflammatory Arthritis Centre vs Arthritis. AVR is a member of the paediatric steering committee of RECOVERY, the steering committee of COVINTOC study and the steering committee of baricitinib in COVID-19.

**Competing interests** AA, AN, HB, FC, GDM, RG, CM-C and JRC have nothing to declare. PMM has received consulting and/or speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche and UCB, all unrelated to this manuscript. G-RRB has received consulting and/or speaker's fees from Abbvie, Gilead, Lilly, Roche, Sanofi, Pfizer all unrelated to this manuscript. IK-P has received consulting and/or speaker's fees from Novartis, SOBI, Amgen, CHUGAI, Pfizer, LFB, Novimmune, Abbvie and PAtent for AIDAI score AVR has received speaker fees/Honoraria from Abbvie, Lilly, Roche, UCB, SOBI and Novartis all unrelated to this manuscript. DGM has received consulting and/or speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche and UCB, all unrelated to this manuscript. XM has received consulting and/or speaker's fees from BMS, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer, Servier and UCB, all unrelated to this manuscript.

**Patient and public involvement statement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study. All data relevant to the study are included in the article or uploaded as online supplemental information.



**ORCID iDs**
Alessia Alunno http://orcid.org/0000-0003-1105-5640
Aurélie Najm http://orcid.org/0000-0002-6008-503X
Pedro M Machado http://orcid.org/0000-0002-8411-7972
Gerd-Rüdiger R Burmester http://orcid.org/0000-0001-7518-1131
Francesco Carubbi http://orcid.org/0000-0003-1958-5136
John D Isaacs http://orcid.org/0000-0002-6103-7056
Isabelle Koné-Paut http://orcid.org/0000-0001-8939-5763
Pier Luigi Meroni http://orcid.org/0000-0002-3394-1451
Luca Quartuccio http://orcid.org/0000-0002-0134-6439
Hendrik Schulze-Koops http://orcid.org/0000-0002-1681-491X
Tanja A Stamm http://orcid.org/0000-0003-3073-7284
Benjamin Terrier http://orcid.org/0000-0001-6612-7336
Xavier Mariette http://orcid.org/0000-0002-4244-5417

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