CLINICAL SCIENCE

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 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.

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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.

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REFERENCES

1 Alunno A, Najm A, Machado PM, *et al*. EULAR points to consider on pathophysiology and use of immunomodulatory therapies in COVID-19. *Ann Rheum Dis* 2021;80:698–706.
2 COVID-19 clinical management: living guidance. Available: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1
3 Coronavirus Disease 2019 (COVID-19)treatment guidelines. Available: https://www.covid19treatmentguidelines.nih.gov/
4 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:74.
5 To KK-W, Sridhar S, Chiu KH-Y, *et al*. Lessons learned 1 year after SARS-CoV-2 emergence leading to COVID-19 pandemic. *Emerg Microbes Infect* 2021;10:507-535.
6 Alunno A, Najm A, Mariette X. Immunomodulatory therapies for SARS-CoV-2 infection: a systematic literature review to inform EULAR points to consider. *Ann Rheum Dis* 2021;80. doi:10.1136/annrheumdis-2020-219725
7 Dabbous HM, El-Sayed MH, El Assal G, *et al*. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: a randomised controlled trial. *Sci Rep* 2021;11:7282.
8 Galan LEB, Santos NMD, Asato MS, *et al*. Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. *Pathog Glob Health* 2021;115:235–42.
9 Ader F, Peiffer-Smadja N, Poissy J, *et al*. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clin Microbiol Infect* 2021. doi:10.1016/j.cmi.2021.05.020. [Epub ahead of print: 26 May 2021].
10 Brown SM, Peltan I, Kumar N, *et al*. Hydroxychloroquine versus azithromycin for hospitalized patients with COVID-19. Results of a randomized, active comparator trial. *Ann Am Thorac Soc* 2021;18:590–7.
11 Reis G, Moreira Silva EADS, Medeiros Silva DC, *et al*. Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19: the together randomized clinical trial. *JAMA Netw Open* 2021;4:e216468.
12 Sivapalan P, Suppli Ulrik C, Sophie Lapperre T, *et al*. Azithromycin and hydroxychloroquine in hospitalised patients with confirmed COVID-19-a randomised double-blinded placebo-controlled trial. *Eur Respir J* 2021. doi:10.1183/13993003.00752-2021. [Epub ahead of print: 03 Jun 2021].
13 Schwartz I, Boesen ME, Cerchiaro G, *et al*. Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial. *CMAJ Open* 2021;9:E693–702.

14 Réa-Neto Álvaro, Bernardelli RS, Câmara BMD, *et al*. An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients. *Sci Rep* 2021;11:9023.
15 Ko JJ, Wu C, Mehta N, *et al*. A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. *J Intensive Care Med* 2021;36:673–80.
16 Rosas IO, Bräu N, Waters M. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med* 2021. doi:10.1056/NEJMoa2028700
17 Soin AS, Kumar K, Choudhary NS, *et al*. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Respir Med* 2021;9:511–21.
18 , Gordon AC, Mouncey PR, *et al*, REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–502.
19 Abani O, Abbas A, Abbas F, *et al*. Tocilizumab in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–45.
20 Mariette X, Hermine O, Tharaux P-L, *et al*. Effectiveness of tocilizumab in patients hospitalized with COVID-19: a follow-up of the CORIMUNO-TOCI-1 randomized clinical trial. *JAMA Intern Med* 2021;181:1241–3. doi:10.1001/jamainternmed.2021.2209
21 , Shankar-Hari M, Vale CL, *et al*, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA* 2021;326:499–518. doi:10.1001/jama.2021.11330
22 Lescure F-X, Honda H, Fowler RA, *et al*. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021;9:522–32.
23 Tharaux P-L, Pialoux G, Pavot A, *et al*. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med* 2021;9:295–304.
24 Kyriazopoulou E, Poulakou G, Milionis H, *et al*. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 2021. doi:10.1038/s41591-021-01499-z. [Epub ahead of print: 03 Sep 2021].
25 Caricchio R, Abbate A, Gordeev I, *et al*. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. *JAMA* 2021;326:230.
26 Tardif J-C, Bouabdallaoui N, L'Allier PL, *et al*. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med* 2021;9:924–32. doi:10.1016/S2213-2600(21)00222-8
27 Lopes MI, Bonjorno LP, Giannini MC, *et al*. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open* 2021;7:e001455.
28 Horby PW, Campbell M. Colchicine in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *MedRxiv* 2021 https://www.medrxiv.org/content/10.1101/2021.05.18.21257267v1
29 Kalil AC, Patterson TF, Mehta AK, *et al*. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;384:795–807.
30 Statement—NIH closes enrollment in trial comparing COVID-19 treatment regimens. Available: https://www.niaid.nih.gov/news-events/statement-nih-closes-enrollment-trial-comparing-covid-19-treatment-regimens
31 Marconi VC, Ramanan AV, de Bono S, *et al*. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (cov-barrier): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021;S2213-2600:00331–3.
32 Guimarães PO, Quirk D, Furtado RH, *et al*. Tofacitinib in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* 2021;385:406–15. doi:10.1056/NEJMoa2101643
33 RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (recovery): a randomised controlled, open-label, platform trial. *Lancet* 2021;397:2049–59.
34 Gottlieb RL, Nirula A, Chen P, *et al*. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA* 2021;325:632.
35 Weinreich DM, Sivapalasingam S, Norton T, *et al*. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384:238–51.
36 Dougan M, Nirula A, Azizad M, *et al*. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med Overseas Ed* (Published Online First: July 2021).
37 A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med* 2021;384. doi:10.1056/NEJMoa2033130
38 Pandit A, Bhalani N, Bhushan BLS, *et al*. Efficacy and safety of pegylated interferon alfa-2b in moderate COVID-19: a phase II, randomized, controlled, open-label study. *Int J Infect Dis* 2021;105:516–21.

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

Online Supplementary Material

Alunno A, *et al. Ann Rheum Dis* 2021;0:1–7. doi: 10.1136/annrheumdis-2021-221366

Online Supplementary Text S1: Search strategy for articles about COVID-19 treatment with immunomodulatory treatment

Medline
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

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

38 (Etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor Fc fusion protein" or "tumour necrosis factor receptor Fc fusion protein").mp. dentifier, synonyms] (2787)
39 Fedratinib.mp. dentifier, synonyms] (61)
40 Filgotinib.mp. dentifier, synonyms] (87)
41 Fingolimod Hydrochloride/ (720)
42 (Fingolimod or gilenia or gilenya).mp. dentifier, synonyms] (1398)
43 (Golimumab or simponi).mp. dentifier, synonyms] (805)
44 (Guselkumab or tremfya).mp. dentifier, synonyms] (234)
45 exp Glucocorticoids/ (21083)
46 glucocorticoid*.mp. dentifier, synonyms] (22665)
47 HCR040.mp. dentifier, synonyms] (0)
48 Hydroxychloroquine/ (1171)
49 (Hydroxychloroquine or plaquenil).mp. dentifier, synonyms] (3003)
50 IFX-1.mp. dentifier, synonyms] (14)
51 Imatinib Mesylate/ (1814)
52 (Imatinib or gleevac or gleevec or glivec).mp. dentifier, synonyms] (4620)
53 exp Immunoglobulins/ (106188)
54 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*).mp. dentifier, synonyms] (50150)
55 exp Immunotherapy/ (44172)
56 (Immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or "BRM therap*" or "immune therap*" or "immunoglobulin therap*" or "immunological therap*" or "immunological treatment*" or "immunomodulatory intervention*").mp. dentifier, synonyms] (48544)
57 IMU-838.mp. dentifier, synonyms] (2)
58 Infliximab/ (2440)
59 (Infliximab or flixabi or inflectra or remicade or remsima or renflexis).mp. dentifier, synonyms] (5286)
60 exp Interferons/ (15621)
61 Interferon*.mp. dentifier, synonyms] (40965)
62 Itolizumab.mp. dentifier, synonyms] (28)
63 Immunoglobulins, Intravenous/ (2436)
64 IVIG.mp. dentifier, synonyms] (2567)
65 (Ixekizumab or taltz).mp. dentifier, synonyms] (510)
66 Jakotinib.mp. dentifier, synonyms] (0)
67 Leflunomide/ (240)
68 (Leflunomide or arava).mp. dentifier, synonyms] (695)
69 Masitinib.mp. dentifier, synonyms] (63)
70 Mast Cells/ (2767)
71 ((mast adj cell*) or mastocyte*).mp. dentifier, synonyms] (7573)
72 Mavrilimumab.mp. dentifier, synonyms] (19)
73 Methotrexate/ (4535)
74 (Methotrexate or metoject or nordimet or novatrex).mp. dentifier, synonyms] (10851)
75 exp Methylprednisolone/ (2121)
76 Methylprednisolone.mp. dentifier, synonyms] (4915)
77 Mycophenolic Acid/ (1248)
78 (Mycophenolate or (mycophenolic adj acid) or myfortic or (mycophenolate adj mofetil)).mp. dentifier, synonyms] (3724)
79 (Nintedanib or intedanib).mp. dentifier, synonyms] (766)
80 exp Anti-Inflammatory Agents, Non-Steroidal/ (24544)

81 (NSAID* or "non steroid anti inflammatory agent*" or "non steroid anti inflammatory drug*" or "non steroidal anti inflammatory agent*" or "non steroidal anti inflammatory drug*" or "nonsteroid antiinflammatory agent*" or "nonsteroid antiinflammatory drug*" or "nonsteroidal antiinflammatory agent*" or "nonsteroidal antiinflammatory drug*" or "non steroid antiinflammatory agent*" or "non steroid antiinflammatory drug*" or "non steroidal antiinflammatory agent*" or "non steroidal antiinflammatory drug*" or "nonsteroid anti inflammatory agent*" or "nonsteroid anti inflammatory drug*" or "nonsteroidal anti inflammatory agent*" or "nonsteroidal anti inflammatory drug*").mp. dentifier, synonyms] (12245)
82 (Ocrelizumab or ocrevus).mp. dentifier, synonyms] (285)
83 Otilimab.mp. dentifier, synonyms] (2)
84 Programmed Cell Death 1 Receptor/ (4857)
85 (PD-1 or Gilvetmab or "programmed cell death 1 receptor").mp. dentifier, synonyms] (13078)
86 (Pembrolizumab or keytruda or lambrolizumab).mp. dentifier, synonyms] (4063)
87 exp Prednisolone/ (4716)
88 Prednisolone.mp. dentifier, synonyms] (7040)
89 Prednisone/ (3337)
90 Prednisone.mp. dentifier, synonyms] (7442)
91 (Ravulizumab or ultomiris).mp. dentifier, synonyms] (29)
92 ((recombinant adj2 "interleukin 2") or lymphocult).mp. dentifier, synonyms] (92)
93 (recombinant adj2 "interleukin 7").mp. dentifier, synonyms] (18)
94 Rituximab/ (4433)
95 (Rituximab or mabthera or truxima).mp. dentifier, synonyms] (10152)
96 (Ruxolitinib or jakafi or jakavi).mp. dentifier, synonyms] (1043)
97 (Sarilumab or kevzara).mp. dentifier, synonyms] (133)
98 (Secukinumab or cosentyx).mp. dentifier, synonyms] (1013)
99 Selinexor.mp. dentifier, synonyms] (163)
100 Siltuximab.mp. dentifier, synonyms] (88)
101 exp Stem Cells/ (56740)
102 "stem cell*".mp. dentifier, synonyms] (126152)
103 Sulfasalazine/ (376)
104 (Sulphasalazine or salazopyrine or sulfasalazine or salazosulfapyridine).mp. dentifier, synonyms] (1086)
105 TD-0903.mp. dentifier, synonyms] (0)
106 (Tocilizumab or roactemra).mp. dentifier, synonyms] (2307)
107 (Tranilast or rizaben).mp. dentifier, synonyms] (144)
108 ("tumor necrosis factor alpha inhibitor*" or "tumour necrosis factor alpha inhibitor*").mp. dentifier, synonyms] (517)
109 ("anti TNF agent*" or "anti TNF alpha agent*").mp. dentifier, synonyms] (834)
110 ("anti tumor necrosis factor agent*" or "anti tumour necrosis factor agent*").mp. dentifier, synonyms] (181)
111 ("TNF alpha inhibitor*" or "TNF inhibitor*").mp. dentifier, synonyms] (1775)
112 ("tumur necrosis factor inhibitor*" or "tumour necrosis factor inhibitor*").mp. dentifier, synonyms] (257)
113 (Upadacitinib or rinvoq).mp. dentifier, synonyms] (116)
114 (Ustekinumab or stelara).mp. dentifier, synonyms] (1401)
115 Ustekinumab/ (605)
116 Vafidemstat.mp. dentifier, synonyms] (1)
117 vMIP.mp. dentifier, synonyms] (20)
118 zilucoplan.mp. dentifier, synonyms] (4)
119 (acalabrutinib or "acp 196" or acp196 or calquence).mp. dentifier, synonyms] (141)

120 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 (506357)
121 exp Coronavirus/ (19595)
122 exp Coronavirus Infections/ (20991)
123 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (38713)
124 "severe acute respiratory syndrome*".ti,ab,kw,kf. (6855)
125 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1388)
126 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (28750)
127 121 or 122 or 123 or 124 or 125 or 126 (51103)
128 120 and 127 (5416)
129 limit 128 to yr="2019 -Current" (3615)

Embase

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

23 exp cell therapy/ (202065)
24 ("cell based therapy" or "cell based therapies" or "cell therapy" or "cell therapies" or "cellular therapy" or "cellular therapies").mp. (68705)
25 Certolizumab.mp. (7209)
26 chloroquine/ (24968)
27 Chloroquin*.mp. (28360)
28 CIGB-258.mp. (0)
29 CMAB806.mp. (0)
30 exp colchicine/ (20097)
31 Colchicine.mp. (21834)
32 exp corticosteroid/ (713138)
33 (corticosteroid* or "adrenal cortex hormone*" or "cortical steroid*" or "cortico steroid*" or corticoid* or "corticosteroid agent*").mp. (254142)
34 cyclosporine/ (12119)
35 Cyclosporin*.mp. (128632)
36 CYT-107.mp. (25)
37 dexamethasone/ (116542)
38 Dexamethasone.mp. (125934)
39 DFV890.mp. (0)
40 ebastine/ (1148)
41 Ebastine.mp. (1181)
42 eculizumab/ (5141)
43 Eculizumab.mp. (5371)
44 etanercept/ (31276)
45 (Etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor Fc fusion protein" or "tumour necrosis factor receptor Fc fusion protein").mp. (32234)
46 fedratinib/ (398)
47 Fedratinib.mp. (413)
48 filgotinib/ (383)
49 Filgotinib.mp. (389)
50 fingolimod/ (9700)
51 (Fingolimod or gilenia or gilenya).mp. (9947)
52 golimumab/ (6880)
53 (Golimumab or simponi).mp. (7051)
54 guselkumab/ (692)
55 (Guselkumab or tremfya).mp. (720)
56 exp glucocorticoid/ (547889)
57 glucocorticoid*.mp. (109216)
58 HCR040.mp. (0)
59 hydroxychloroquine/ (23249)
60 (Hydroxychloroquine or plaquenil).mp. (24266)
61 IFX-1.mp. (95)
62 imatinib/ (41910)
63 (Imatinib or gleevac or gleevec or glivec).mp. (43723)
64 exp immunoglobulin/ (373027)
65 (Immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*).mp. (568468)
66 exp immunotherapy/ (191127)
67 (Immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or "BRM therap*" or "immune therap*" or "immunoglobulin therap*" or "immunological therap*" or "immunological treatment*" or "immunomodulatory intervention*").mp. (182967)

68 IMU-838.mp. (8)
69 infliximab/ (50638)
70 (Infliximab or flixabi or inflectra or remicade or remsima or renflexis).mp. (51789)
71 exp interferon/ (499113)
72 Interferon*.mp. (339214)
73 itolizumab/ (77)
74 IVIG.mp. (16952)
75 ixekizumab/ (1706)
76 (Ixekizumab or taltz).mp. (1763)
77 Jakotinib.mp. (0)
78 leflunomide/ (11660)
79 (Leflunomide or arava).mp. (11973)
80 masitinib/ (507)
81 Masitinib.mp. (537)
82 mast cell/ (32134)
83 ((mast adj cell*) or mastocyte*).mp. (44865)
84 mavrilimumab/ (110)
85 Mavrilimumab.mp. (110)
86 methotrexate/ (138928)
87 (Methotrexate or metoject or nordimet or novatrex).mp. (142684)
88 methylprednisolone/ (78064)
89 Methylprednisolone.mp. (85801)
90 mycophenolic acid/ (17362)
91 (Mycophenolate or (mycophenolic adj acid) or myfortic or (mycophenolate adj mofetil)).mp. (68499)
92 nintedanib/ (3037)
93 (Nintedanib or intedanib).mp. (3252)
94 exp nonsteroid antiinflammatory agent/ (580879)
95 (NSAID* or "non steroid anti inflammatory agent*" or "non steroid anti inflammatory drug*" or "non steroidal anti inflammatory agent*" or "non steroidal anti inflammatory drug*" or "nonsteroid antiinflammatory agent*" or "nonsteroid antiinflammatory drug*" or "nonsteroidal antiinflammatory agent*" or "nonsteroidal antiinflammatory drug*" or "non steroid antiinflammatory agent*" or "non steroid antiinflammatory drug*" or "non steroidal antiinflammatory agent*" or "non steroidal antiinflammatory drug*" or "nonsteroid anti inflammatory agent*" or "nonsteroid anti inflammatory drug*" or "nonsteroidal anti inflammatory agent*" or "nonsteroidal anti inflammatory drug*").mp. (131423)
96 ocrelizumab/ (1735)
97 (Ocrelizumab or ocrevus).mp. (1805)
98 otilimab/ (17)
99 Otilimab.mp. (17)
100 gilvetmab/ (251)
101 (PD-1 or Gilvetmab).mp. (31251)
102 programmed cell death 1 receptor.mp. (221)
103 pembrolizumab/ (15300)
104 (Pembrolizumab or keytruda or lambrolizumab).mp. (16207)
105 prednisolone/ (97691)
106 Prednisolone.mp. (108112)
107 prednisone/ (127911)
108 Prednisone.mp. (132005)
109 ravulizumab/ (93)
110 (Ravulizumab or ultomiris).mp. (96)

111 exp recombinant interleukin 2/ (5784)
112 ((recombinant adj2 "interleukin 2") or lymphocult).mp. (4146)
113 exp recombinant interleukin 7/ (339)
114 (recombinant adj2 "interleukin 7").mp. (363)
115 rituximab/ (79475)
116 (Rituximab or mabthera or truxima).mp. (83435)
117 ruxolitinib/ (4756)
118 (Ruxolitinib or jakafi or jakavi).mp. (4910)
119 sarilumab/ (594)
120 (Sarilumab or kevzara).mp. (615)
121 secukinumab/ (3533)
122 (Secukinumab or cosentyx).mp. (3646)
123 selinexor/ (664)
124 Selinexor.mp. (699)
125 siltuximab/ (687)
126 Siltuximab.mp. (706)
127 exp stem cell/ (362533)
128 (Stem adj cell*).mp. (538786)
129 salazosulfapyridine/ (19864)
130 (Sulphasalazine or salazopyrine or sulfasalazine or salazosulfapyridine).mp. (20375)
131 TD-0903.mp. (1)
132 tocilizumab/ (12168)
133 (Tocilizumab or roactemra).mp. (12676)
134 tranilast/ (1181)
135 (Tranilast or rizaben).mp. (1222)
136 exp tumor necrosis factor inhibitor/ (90671)
137 ("tumor necrosis factor alpha inhibitor*" or "tumour necrosis factor alpha inhibitor*").mp. (6793)
138 ("anti TNF agent*" or "anti TNF alpha agent*").mp. (4699)
139 ("anti tumour necrosis factor agent*" or "anti tumor necrosis factor agent*").mp. (582)
140 ("TNF alpha inhibitor*" or "TNF inhibitor*").mp. (7426)
141 ("tumour necrosis factor inhibitor*" or "tumor necrosis factor inhibitor*").mp. (14939)
142 upadacitinib/ (408)
143 (Upadacitinib or rinvoq).mp. (417)
144 ustekinumab/ (7049)
145 (Ustekinumab or stelara).mp. (7247)
146 vafidemstat/ (6)
147 Vafidemstat.mp. (6)
148 vMIP.mp. (139)
149 zilucoplan/ (25)
150 zilucoplan.mp. (25)
151 itolizumab.mp. (81)
152 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or

131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 (3020762)
153 exp Coronavirinae/ (16754)
154 exp Coronavirus infection/ (17958)
155 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (35694)
156 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (1168)
157 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (37658)
158 "severe acute respiratory syndrome*".ti,ab,kw. (9296)
159 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (33830)
160 153 or 154 or 155 or 156 or 157 or 158 or 159 (64189)
161 152 and 160 (9143)
162 limit 161 to yr="2019 -Current" (5942)

CINAHL

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

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S35 OR S36 OR S37 OR
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S41 OR S42 OR S43 OR
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S47 OR S48 OR S49 OR
S50 OR S51 OR S52 OR
S53 OR S54 OR S55 OR
S56 OR S57 OR S58 OR
S59 OR S60 OR S61 OR
S62 OR S63 OR S64 OR
S65 OR S66 OR S67 OR
S68 OR S69 OR S70 OR
S71 OR S72 OR S73 OR
S74 OR S75 OR S76 OR
S77 OR S78 OR S79 OR
S80 OR S81 OR S82 OR
S83 OR S84 OR S85 OR
S86 OR S87 OR S88 OR
S89 OR S90 OR S91 OR
S92 OR S93 OR S94 OR
S95 OR S96 OR S97 OR
S98 OR S99 OR S100
OR S101 OR S102 OR
S103 OR S104 OR S105
OR S106 OR S107 OR
S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114

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

S93 (recombinant N2 "interleukin 7")
S92 (recombinant N2 "interleukin 2") or lymphocult
S91 ravulizumab or ultomiris
S90 prednisone
S89 (MH "Prednisone")
S88 prednisolone
S87 (MH "Prednisolone")
S86 pembrolizumab or keytruda or lambrolizumab
S85 PD-1 or gilvetmab or "programmed cell death 1 receptor"
S84 (MH "Programmed Cell Death Protein 1 Receptor")
S83 otilimab
S82 ocrelizumab or ocrevus
S81 ((nonsteroid* or “non steroid*”) adj (antiinflammatory or “anti inflammatory”) adj (drug* or agent*)) or NSAID*)
S80 (MH "Antiinflammatory Agents, Non-Steroidal")
S79 nintedanib or intedanib
S78 mycophenolate or "mycophenolic acid" or "mycophenolate mofetil" or myfortic
S77 (MH "Mycophenolic Acid") OR (MH "Mycophenolate Mofetil")
S76 methylprednisolone
S75 (MH "Methylprednisolone")
S74 methotrexate or metoject or nordimet or novatrex
S73 (MH "Methotrexate")
S72 mavrilimumab
S71 (MH "Mast Cells")
S70 "mast cell*" or mastocyte*
S69 mastinib
S68 leflunomide or arava
S67 (MH "Leflunomide")
S66 jakotinib
S65 ixekizumab or taltz
S64 IVIG
S63 (MH "Immunoglobulins intravenous")
S62 itolizumab
S61 Interferon*
S60 (MH "Interferons")
S59 "infliximab or flixabi or inflectra or remicade or remsima or renflexis
S58 (MH "Infliximab”)
S57 IMU-838
S56 immunotherap* or "biologic response modifier therap*" or "biological response modifier therap*" or BRM therap*" or "immune therap*" or "immunoglobulin therap*"or "immunological therap*" or "immunological treatment*" or "immunological intervention*"
S55 (MH "Immunotherapy")
S54 immunoglobulin* or "gamma-globulin*" or gammaglobulin* or tegeline or veinoglobulin* or venoglobulin*
S53 (MH "Immunoglobulins")
S52 imatinib or gleevac or gleevec or glivec
S51 (MH "Imatinib")
S50 IFX-1
S49 hydroxychloroquine or plaquenil
S48 (MH"Hydroxychloroquine")
S47 HCR040

S46 glucocorticoid*
S45 (MH "Glucocorticoids+")
S44 guselkumab or tremfya
S43 golimumab or simponi
S42 (MH "Golimumab")
S41 fingolimod or gilenia or
gilenya
S40 filgotinib
S39 fedratinib
S38 etanercept or benepali or embrel or enbrel or "tumor necrosis factor receptor fc fusion protein" or "tumour necrosis factor receptor fc fusion protein"
S37 (MH "Etanercept")
S36 eculizumab
S35 ebastine
S34 DFV890
S33 dexamethasone
S32 (MH "Dexamethasone")
S31 CYT-107
S30 cyclosporin
S29 (MH "Cyclosporine")
S28 corticosteroid* or"adrenal cortex hormone*" or "cortical steroid*" or "corticosteroid*" or corticoid* or "corticosteroid agent*"
S27 (MH "Adrenal Cortex Hormones+")
S26 colchicine
S25 (MH "Colchicine")
S24 CMAB806
S23 CIGB-258
S22 chloroquin*
S21 (MH "Chloroquine+")
S20 certolizumab
S19 (MH “Cell Therapy”)
S18 "cell based therap*" or "cell therap*" or "cellular therapy**
S17 canakinumab or ilaris
S16 brensocatib
S15 bevacizumab or avastin
S14 (MH "Bevacizumab")
S13 BDB-001
S12 baricitinib or olumiant
S11 azathioprine or arathioprin or arathioprine or immurel or imurel
S10 TD-0903
S9 advoralimab
S8 ARGX-117
S7 anakinra or kineret of "recombinant interleukin 1 receptor antagonist" or "recombinant interleukin 1 receptor blocker" or recombinant interleukin 1 receptor blocking agent"
S6 adalimumab or adaly or amgevita or amjevita or humira or imraldi or trudexaS5 (MH "Adalimumab")
S4 acalabrutinib or "acp196" or acp196 or calquence
S3 (ABX464
S2 (MH "Abatacept")
S1 abatacept or "CTLA4 Ig" or "CTLA4 immunoglobulin" or orencia

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Comment: Cochrane - CENTRAL

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

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

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

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

Online Supplementary Text S2: Search strategy for articles about COVID-19 treatment with anti-SARS-CoV2 monoclonal antibodies

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

1 exp Coronavirus/ 71936
2 exp Coronavirus Infections/ 91546
3 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. 145307
4 "severe acute respiratory syndrome*".ti,ab,kw,kf. 18569
5 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. 3312
6 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. 84804
7 1 or 2 or 3 or 4 or 5 or 6 158270
8 bamlanivimab.mp. 56
9 LY-CoV555.mp. 17
10 LYCoV555.mp. 0
11 LY3819253.mp. 3
12 LY-3819253.mp. 1
13 etesevimab.mp. 16
14 LY-CoV016.mp. 8
15 LYCoV016.mp. 3
16 LY3832479.mp. 2
17 LY-3832479.mp. 1
18 casirivimab.mp. 33
19 REGN10933.mp. 9
20 REGN-10933.mp. 1
21 imdevimab.mp. 34
22 REGN10987.mp. 10
23 REGN-10987.mp. 1
24 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 86
25 7 and 24 84
26 limit 25 to yr="2020 -Current" 80
27 from 26 keep 1-80 80

Embase

1 exp Coronavirinae/ 55059
2 exp Coronavirus infection/ 145737
3 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. 131138
4 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.2831
5 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or

COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. 143698
6 "severe acute respiratory syndrome*".ti,ab,kw. 22063
7 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. 91974
8 1 or 2 or 3 or 4 or 5 or 6 or 7 182654
9 bamlanivimab.mp. 98
10 LY-CoV555.mp. 19
11 LYCoV555.mp. 1
12 LY3819253.mp. 3
13 LY-3819253.mp. 4
14 etesevimab.mp. 33
15 LY-CoV016.mp. 6
16 LYCoV016.mp. 1
17 LY3832479.mp. 1
18 LY-3832479.mp. 1
19 casirivimab.mp. 50
20 REGN10933.mp. 12
21 REGN-10933.mp. 6
22 imdevimab.mp. 50
23 REGN10987.mp. 12
24 REGN-10987.mp. 7
25 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 130
26 8 and 25 125
27 limit 26 to yr="2020 -Current" 125

Cochrane Library
#1 MeSH descriptor: [Coronavirus] 1 tree(s) exploded 4
#2 MeSH descriptor: [Coronavirus Infections] explode all trees 984
#3 (((corona* or corono*) near/1 (virus* or viral* or virinae*))):ti,ab,kw 244
#4 ((coronavirus* or coronovirus* or coronavirinae* or CoV)):ti,ab,kw 3868
#5 (("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid)):ti,ab,kw 6212
#6 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes") 1076
#7 {or #1-#6} 6579
#8 (bamlanivimab):ti,ab,kw 6
#9 (LY-CoV555):ti,ab,kw 0
#10 (LYCoV555):ti,ab,kw 8
#11 (LY3819253):ti,ab,kw 6
#12 (LY-3819253):ti,ab,kw 0

#13	(etesevimab):ti,ab,kw 3	
#14	(LY-CoV016):ti,ab,kw	0
#15	(LYCoV016):ti,ab,kw	3
#16	(LY3832479):ti,ab,kw	4
#17	(LY-3832479):ti,ab,kw	0
#18	(casirivimab):ti,ab,kw3	
#19	(REGN10933):ti,ab,kw	6
#20	(REGN-10933):ti,ab,kw	0
#21	(imdevimab):ti,ab,kw 3	
#22	(REGN10987):ti,ab,kw	6
#23	(REGN-10987):ti,ab,kw	0
#24	{or #8-#23}	26
#25	#7 and #24 with Publication Year from 2020 to present, in Trials	23

Cinahl

S1	(MH "Coronavirus Infections+")	28,707
S2	("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").	19,496
S3	((corona* or corono*) N1 (virus* or viral* or virinae*)).	514
S4	(coronavirus* or coronovirus* or coronavirinae* or CoV)	22,463
S5	("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid)	57,128
S6	"severe acute respiratorysyndrome*"	6,018
S7	(MH "Coronavirus+")	2,081
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	63,114
S9	"bamlanivimab"	16
S10	"LY-CoV555" or LYCoV555	3
S11	"LY3819253" or LY-3819253	0
S12	"etesevimab"	5
S13	"LY-CoV016" or LYCoV016	0
S14	"LY3832479" or LY-832479	0
S15	casirivimab	7
S16	"REGN10933" or REGN-10933	0
S17	"imdevimab"	7
S18	"REGN10987" or REGN-10987	0

S19	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	21
S20	S8 AND S19	21
S21	S8 AND S19 Limiters - Published Date: 20200101-	21

S1	(MH "Coronavirus Infections+")	28,707
S2	("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").	19,496
S3	((corona* or corono*) N1 (virus* or viral* or virinae*)).	514
S4	(coronavirus* or coronovirus* or coronavirinae* or CoV)	22,463
S5	("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid)	57,128
S6	"severe acute respiratorysyndrome*"	6,018
S7	(MH "Coronavirus+")	2,081
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	63,114
S9	"bamlanivimab"	16
S10	"LY-CoV555" or LYCoV555	3
S11	"LY3819253" or LY-3819253	0
S12	"etesevimab"	5
S13	"LY-CoV016" or LYCoV016	0
S14	"LY3832479" or LY-3832479	0
S15	"casirivimab"	7
S16	"REGN10933" or REGN-10933	0
S17	"imdevimab"	7
S18	"REGN10987" or REGN-10987	0
S19	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	21
S20	S8 AND S19	21
S21	S8 AND S19 Limiters - Published Date: 20200101-	21

Update: Using rheumatology drugs for COVID-19

This is the lay version of the EULAR points to consider on the use of medicines traditionally used in rheumatology to treat the inflammation seen in people with severe COVID-19. The original publication can be downloaded from the EULAR website: www.eular.org.

Alunno A, et al. 2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19. Ann Rheum Dis 2021;80:221–366. doi:10.1136/annrheumdis-2021-221366

Introduction

EULAR recommendations give advice to doctors, nurses and patients about the best way to treat and manage diseases. EULAR has updated the points on the pathophysiology of COVID-19 and the use of immunomodulatory therapies to treat it. Based on the low level of evidence available for this topic, it was not possible to develop full recommendations, and the work has been presented instead as 'points to consider'.

Doctors, other health professionals and patients worked together to develop this advice. The patients in the team ensured that the patient point of view was included. The authors looked at the evidence on COVID-19 infection, and the use of different therapies that act on the immune system.

What do we already know?

COVID-19 is the disease caused by infection with the SARS-CoV-2 virus. Since it emerged at the end of 2019, this virus has caused a global pandemic. COVID-19 can be mild, or even without symptoms at all. But it can also cause severe disease, leading to respiratory problems, organ failure, and death. Research on the immune mechanisms involved in people with severe COVID-19 has shown that they have widespread inflammation.

Many medicines used in rheumatology are anti-inflammatory or immunomodulatory drugs. They are designed to treat the inflammation caused by autoimmune diseases such as rheumatoid arthritis, where the body's immune systems attacks its own tissues. New research is looking at how these medicines might be used to treat people with COVID-19. EULAR previously provided a framework to optimize the use of immunomodulatory therapies for the care of people with COVID-19. The first EULAR-endorsed points to consider on this topic were developed in 2020. Evidence is changing very quickly, and the points have been updated to include the most recent literature available.

These findings do not apply to people living with rheumatic and musculoskeletal diseases (RMDs) who are taking immunomodulatory treatments for their rheumatic disease. Separate recommendations are available for the management of people with RMDs in the context of the pandemic.

What do the points say?

In total, there are two overarching principles and 12 points to consider. The principles are unchanged from the earlier publication, and stress that the picture of SARS-CoV-2 infection can be very different in different people. Infections range from asymptomatic or mild disease to severe or fatal. People with COVID-19 may need different treatment approaches, including antiviral medicines, oxygen therapy, anticoagulation and/or immunomodulatory treatment at different stages of the disease.

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The 12 points to consider focus on immunomodulatory therapy, and how we might use existing medicines from the field of rheumatology to treat severe COVID-19. Overall, 4 of the 12 points are unchanged from the 2020 version, 4 are modified, and 4 are new. WHO has validated the use of two types of immunomodulators in severe and critical COVID-19: corticosteroids and anti-IL-6 receptor antibodies.

Each point is based on the best current knowledge and studies of scientific evidence or expert opinion. The more stars a point has the stronger the evidence is. However, points to consider with limited scientific evidence may still be important, because the experts can have a strong opinion even when the published evidence may be lacking.

One star (*) means it is a point with limited scientific evidence.

Two stars (**) means it is a point with some scientific evidence.

Three stars (***) means it is a point with quite a lot of scientific evidence.

Four stars (****) means it is a point supported with a lot of scientific evidence.

- **In people with COVID-19 who do not need hospitalisation, there is currently no evidence to support using an immunomodulatory therapy.*** (unchanged)**
  Mild or moderate COVID-19 that does not require hospitalisation does not respond to immunomodulatory medicines. At the moment, the evidence suggests that these work only for severe COVID-19 where there is a severe systemic inflammatory state. Research is looking at anti-viral medicines to treat people outside the hospital setting.

- **In people hospitalised for COVID-19 who do not need oxygen therapy there is currently no evidence to support starting immunomodulatory therapy.*** (unchanged)**
  There is no evidence to support using immunomodulatory drugs in people hospitalised for COVID-19 if they do not need oxygen therapy. For those who do need oxygen, there are specific guidelines below.

- **In people with COVID-19 who need supplemental oxygen or ventilation, systemic glucocorticoids should be used since they can decrease mortality.*** (unchanged)**
  For people who are in hospital because of COVID-19 and need to be given oxygen – or need ventilation to help them breathe – there is evidence that using immunomodulatory glucocorticoids can reduce the number of people who die. The drug with the most evidence to support this is dexamethasone, which is a steroid that can help to reduce inflammation.

- **Hydroxychloroquine should be avoided for treating any stage of COVID-19.*** (unchanged)**
  Early on the in the pandemic, a rheumatology drug called hydroxychloroquine was proposed as a possible treatment. However, the evidence does not support this. It does not look like hydroxychloroquine provides any additional benefit to the standard of care, and could worsen the prognosis in more severe infections, particularly if given with azithromycin.

- **In people with COVID-19 who require oxygen or ventilation, combination treatment with glucocorticoids and tocilizumab should be considered.*** (modified)**
  A combination of glucocorticoids and tocilizumab can reduce disease progression and mortality in COVID-19. More data are needed to fully appreciate the effect of other IL-6R inhibitors.

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- **There is no robust evidence to support the use of anakinra at any disease stage.*** (modified)**
  There has been conflicting evidence about the use of anakinra for people with severe COVID-19, and nothing to support its use in any stage of COVID-19.

- **There is no robust evidence to support the use of low-dose colchicine at any disease stage.*** (new)**
  Since the 2020 publication, there has been new evidence from two trials, but the results were not solid enough to recommend in favour of colchicine.

- **In people with COVID-19 who need non-invasive ventilation or high-flow oxygen, the combination of glucocorticoids and baricitinib or tofacitinib could be considered.*** (modified)**
  Baricitinib or tofacitinib can decrease the time to recovery and speed up improvement, and can be considered in some people with severe COVID-19 who need non-invasive ventilation or high-flow oxygen to help them breathe.

- **Ongoing trials mean it is not possible to recommend the use of GM-CSF inhibitors in COVID-19.*** (new)**
  GM-CSF inhibitors (mavrilimumab, otilimab, and lenzilumab) are being investigated in clinical trials, but there is not yet enough evidence to recommend their use to treat COVID-19.

- **People <u>without</u> hypogammaglobulinaemia and with symptom onset more than 5 days ago should not be given convalescent plasma.*** (new)**
  Hypogammaglobulinaemia is a state where a person has low plasma gamma globulins and impaired antibody formation. For people whose COVID-19 symptoms started more than 5 days ago, and who do not have hypogammaglobulinaemia there is robust evidence against the use of convalescent plasma.

- **Monoclonal antibodies against antispike protein should be considered in people at risk of severe COVID-19 who are seronegative or whose symptoms started less than 5 days ago.*** (new)**
  Some new drugs have been developed that target a particular protein on the virus called a spike protein. These include bamlanivimab, etesevimab, casirivimab and imdevimab. Trial data suggest these drugs can significantly reduce viral load, but efficacy depends on the virus variant, as well as how long ago symptoms started.

- **There is not enough evidence to recommend the use of other immunomodulators in COVID-19.** (modified)**
  There currently not enough evidence to recommend the use of other immunomodulators to treat people with COVID-19. This includes interferon alpha, interferon beta, interferon kappa, interferon lambda, leflunomide, nonSARS CoV-2 IVIg, eculizumab and cyclosporine. No recommendation either in favour or against the use of these medicines can be made at this point. Other medicines are being investigated, but only those with published evidence are included here.

Summary

Overall, the points give guidance on how to use existing anti-inflammatory, immunomodulatory therapies to treat COVID-19. EULAR hopes these will be a useful reference for health professionals involved in the care of people with SARS-CoV-2 infection. They should be used alongside local regulations and guidelines, and information from bodies such as the World Health Organization.

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Points to consider with just one or two stars are based mainly on expert opinion and not backed up by studies, but these may be as important as those with three or four stars.

If you have any questions or concerns, you should speak to a health professional involved in your care.

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