Is there a role for immune-enhancing therapies for acutely ill patients with coronavirus disease 2019?

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Purpose of review
Although the so-called cytokine storm has been early described and related to a dramatic evolution in severe COVID-19 patients, it soon became clear that those patients display clinical and biological evidence of an immunosuppressive state characterized, among other, by a profound lymphopenia. The negative role of this immune suppression on the outcome raises the question on immune therapies that might improve patient's condition.

Recent findings
Important positive effects of active immune therapies, such as IL-7 or thymosin-α are already described and warrant confirmation in larger prospective trials. For other therapies, such as interferons, firm conclusions for critically ill COVID-19 patients are lacking as those patients were often excluded from the published trials. Treatment with immunoglobulins or convalescent plasma is a passive strategy to provide specific immunity. Unfortunately, results from large RCTs do not support their use presently.

Summary
In this article, we provide a review on active and passive immune boosting strategies that might help treating the most severe COVID-19 patients. We mainly focus on active strategies that include IL-7, thymosin-α, interferons, and vitamin D. Although some positive effects are described, they certainly warrant confirmation in large randomized controlled trials.

Keywords
coronavirus disease 2019, IL-7, immunosuppression, interferon, thymosin-α, vitamin D

INTRODUCTION

The initial description of the coronavirus disease-2019 (COVID-19) pathophysiology put forward a prominent role of the so-called cytokine storm, a condition previously described in other pathological states after some treatments, such as chimeric antigen receptor T (CAR-T) cells infusion. However, although median value of IL-6 in patients with COVID-19 with Acute Respiratory Distress Syndrome (ARDS) is reportedly high, it does not reach those described in non-COVID-19 ARDS patients or peak IL-6 level found in patients who develop Cytokine Release Syndrome after CAR-T cells infusion [1].

Another paradigm of the disease soon emerged: a concomitant immunodeficiency involving among other a (profound) decreased lymphocyte count and an impaired type-I interferon response [2,3]. Lymphopenia occurs in up to 68–80% of patients [3,4], is correlated to severity [4], and involves all subsets including CD4+ and CD8+ cytotoxic T cells, natural killer (NK) cells, memory and regulatory T cells along with B cells [3,5]. Furthermore, blood mononuclear cells obtained from COVID-19 patients produce lower levels of cytokines upon stimulation than those from septic or nonseptic critically ill patients [5], consistent with a marked impairment of immune effector cell function.

Hence, any therapy that might improve immune function and the COVID-19 related immune suppression warrant attention. They may be classified into two major modes of action: therapies that directly improve immune function (IL7, thymosin alpha, etc.) and those therapies providing immune support (immunoglobulins, convalescent plasma, etc.)

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KEY POINTS

- A 'cytokine storm' with markers of acute inflammation was thought to be the major pathophysiologic event in COVID-19 patients. It soon became obvious that immunodeficiency characterized among other by a profound lymphopenia was also a hallmark of severe COVID-19.
- Treatment of this CRIS (for COVID-19-related immune suppression) could include either direct or indirect immune boosters.
- Reports on the effects of IL-7, thymosin-α, vitamin D, and interferons look promising for some of them but we clearly need larger randomized controlled trials to draw firm conclusions.
- Reports on passive immune booster (such as convalescent plasma) are currently disappointing but several studies are still under way.

ACTIVE IMMUNE ENHANCING THERAPIES

Interleukin-7

Interleukin-7 (IL-7), a common γ-chain pleiotropic cytokine, displays various properties including the prevention of lymphocyte apoptosis, the induction of CD4+ and CD8+ T-cell proliferation and the improvement of lymphocyte function. It has, therefore, been proposed in various pathological states including patients with cancer, hematopoietic stem cell transplantation, AIDS, mycobacterial infection, multiple sclerosis, inflammatory bowel disease [6]. IL-7 has been tested in various models of infection and sepsis and in a recent prospective, multicenter, randomized, double-blind, placebo-controlled phase IIb trial in patients with septic shock and severe lymphopenia [7]. With a dose of 10 μg/kg CYT107 (a glycosylated recombinant human IL-7) twice a week for a total of 4 weeks, treated patients displayed an increased absolute lymphocyte count persisting after the end of treatment. An initial transient decrease followed by a significant increase in CD4+ and CD8+ T cells, and, a decreased IL-7 receptor α (CD127) expression on CD4+ and CD8+ T cells were described. Treatment related adverse effect included reversible 'at the site of injection' skin reaction consisting of a raised red rash characterized by a CD3-positive lymphocytic infiltration in skin biopsies [7].

Recently, Laterre *et al.* [8▪] reported on a case series of 12 patients with COVID-19 and severe lymphopenia (defined as two consecutive absolute lymphocyte counts of less than 700/μl) treated with an initial safety dose of 3 μg/kg, followed by a dose of 10 μg/kg by intramuscular injection twice a week for 2 weeks. Treated patients were matched to 13 patients presenting similar severity of illness and comorbidities. As described by François *et al.*, an initial decrease followed by an increase in total lymphocyte count was observed with significant differences starting from day 15 after the first injection and reaching levels more than two-fold greater than the control group. IL-7 was well tolerated without any significant change in clinical (temperature, blood pressure, or PaO_2 : FiO_2 ratio) or biological variables (tumor necrosis factor α, IL-1β, IL-12p70, or IL-6 concentrations). Secondary infections were less frequent but, as in the previous study [7], this study was not powered to detect such difference.

Monneret *et al.* [9] provided compassionate IL-7 to a 74 years old COVID patient who presented severe immunosuppression (assessed by HLA-DR and persisting lymphopenia) and recurrence of nosocomial infections, including Aspergillus fumigatus-related ventilator-associated pneumonia. After an inaugural injection of 3 μg/kg, the patient received 10 μg/kg injections twice a week for 4 weeks. Improvement in total lymphocyte count (including CD4+ cells and NK cells) and mHLA-DR expression toward reference ranges was rapidly observed. Likewise, the IFN score started to decrease while circulating IFN-γ returned to normal range, without any increase in cytokine levels, such as IL-6, IFN-γ, IL-10, or TNF-α.

Taken together, those data suggest IL7 not only improves lymphocyte count but also restores lymphocyte function. Further studies are urgently warranted to confirm these potential benefits. Interestingly, some raise the hypothesis that the positive outcome of dexamethasone might, partially at least, be explained by its capacity to enhance levels of the IL-7 receptor α [10].

Thymosin-alpha

Thymosin alpha1 (Tα1), originally isolated from the thymus, is a peptide of 28 amino acids, sharing similarities with IL-7 [11]. It is used worldwide as an immunomodulatory agent in a wide range of clinical indications, such as for the treatment of chronic hepatitis B and C, and, as a vaccine enhancer. Pharmacological studies showed that Tα1 stimulates endogenous IFN-γ secretion and enhances T cells and the whole immune system by stimulating innate and adaptive immune responses [11].

Previous meta-analysis [12] and review of the literature [13] confirmed reduced mortality and modulation of immunity with increased level of HLA-DR, and improvement of lymphocyte subsets

(CD3 and CD4) and cytokines (IL-6, IL-10 and TNF-α) in septic patients.

The efficacy of Tα1 was assessed *ex vivo* in blood samples drawn from COVID-19 patients and incubated for 8 h with 50 μg/ml Tα1 (SciClone Pharmaceuticals) [14]. The authors demonstrate Tα1 affects genes associated with immune response, inflammation, and response to infection pathways. Moreover, Tα1 decreases some Cytokine-Related Gene Transcriptional Expression found to have a higher transcriptional expression in COVID-19 patients including IL-6, IL-1β, and TNFα. At the opposite, some other genes (such as *IL-10*) were upregulated. Finally, the authors show Tα1 inhibits lymphocyte activation specifically in a CD8+ T cell [14].

In a retrospective study of 76 patients classified as severe or critical COVID-19 patients from two hospitals in Wuhan, China, 36 patients received subcutaneous injections of 1.6 mg Tα1 once a day for at least 7 consecutive days while 40 patients received usual cares [15▪]. Decreased mortality and lower need for invasive mechanical ventilation are observed in the treated patients while an effective restored T-cell numbers is also described only for those patients presenting with lymphopenia (counts of CD8+ T cells or CD4+ T cells lower than 400 or 650/μL, respectively).

Finally, results from a prospective randomized trial performed in Rhodes Island Hospital are awaited (NCT04487444). This study aims at recruiting 80 participants presenting with COVID-19 infection and lymphopenia. The primary objective is to demonstrate an improved time to recovery and the secondary objective will assess the improvement in severity of infection. Treatment protocol is similar to the Chinese study, that is, Ta1 (1.6 mg) administered subcutaneously (s.c.) daily for 1 week.

Interestingly, some authors hypothesized that Tα1, thanks to its potential to stimulate IFN-γ secretion, might also be of benefit in patients developing pulmonary aspergillosis after Sars-Cov-2 infection [16]. This, of course, warrants further studies.

Interferons

Interferons (IFN), produced by leucocytes, T lymphocytes, and fibroblasts, act as a 'first alarm bell' effector of the host immune response during viral infection. There are three main types of IFNs: types I (including alpha and beta), II (gamma), and III (lambda), type I being the largest IFN class. Through activation of various IFN-stimulated genes (ISG), type I IFN display several roles and functions, such as direct antiviral action, inhibition of cellular proliferation, immunomodulation, and desensitization after activation of immune response [17].

Interestingly, Hadjadj *et al.* demonstrated in COVID-19 patients a severity-related impaired IFN type I response associated with a persistent blood viral load, an exacerbated inflammatory response and a lower IFN activity in serum from severe or critical patients as compared with mild-to-moderate patients [18]. The persistence of these effects over time was confirmed by others in critically ill COVID-19 patients with ARDS [19]. These observed dysregulated IFN responses suggest the effective immunomodulatory strategies used by coronaviruses [20] and certainly raise the hypothesis of a potential therapeutic effect of IFN.

While type-I IFN is being evaluated in a large number of trials, either alone or in combination, study design, studied population, and outcomes are very variables.

In a first randomized trial, IFN β-1a, administered subcutaneously at a dose of 12 million IU/ml three times weekly for two consecutive weeks, was superior in terms of 28-day mortality [21]. This conclusion is limited by the small sample size (92), confounding factors (more steroids and intravenous immunoglobulins in patients receiving IFN) and the absence of benefit in other outcomes, such as hospital and ICU length of stay or duration of mechanical ventilation. Interestingly, early administration looked more favorable in terms of reduced mortality.

In the COVIFERON trial, Alavi Darazam *et al.* [22▪] randomized 60 patients to receive on top of standard of cares (oral Lopinavir/Ritonavir and a single dose of 400 mg hydroxychloroquine on the first day), either IFNβ1a (subcutaneous injections of 12 000 IU on days 1, 3, 6), IFNβ1b (subcutaneous injections of 8 000 000 IU on days 1, 3, 6) or placebo. 75 percent of the patients were in ICU and 35% were on mechanical ventilation. The primary endpoint, defined as the time from enrollment to discharge from hospital or a decline of two steps on a seven-step ordinal scale, was reached 2 days earlier for both treated groups (5 versus 7), reaching statistical significance when both treated groups were analyzed together and for IFNβ1a when each group were analyzed separately. However, despite mortality rate in the control group was more than two-fold higher than that of the IFNβ1a group, mortality difference did not reach statistical significance.

In another double-blind, placebo-controlled, phase 2 pilot trial at nine sites in the UK, 101 patients were randomized to assess the efficacy of a 6 MIU inhaled interferon beta-1a formulation (SNG001) in patients admitted to hospital [23]. Although the primary outcome (defined as change in clinical condition on the WHO Ordinal Scale for

Clinical Improvement) reached statistical significance, it is unclear if those results may be translated to critical care patients as only 67% of the patients received oxygen and only 2% required oxygenation through HFNC. The odds of improvement were more than two-fold greater in the SNG001 group on day 15 or 16 and more than three-fold greater on day 28 but treated patients did not present a decreased likelihood of intubation or time to intubation or death.

An open-label, randomized clinical trial also assessed the efficacy of 250 μg subcutaneous IFN β-1b administration every other day for two consecutive weeks [24]. Despite effective in shortening the time to clinical improvement and decreasing admission in ICU and need for invasive mechanical ventilation, the translation of those results to critical COVID-19 patients warrant further evaluation as only three patients required HFNC or NIV at the time of randomization.

Results from other ongoing trials (such as NCT04449380 [25]) will be available soon. However, the most severe patients [such as those requiring mechanical ventilation (MV)] are often excluded from those studies [25].

Interferon lambdas or type III IFN display similar antiviral effect than IFN alfa or beta but use a distinct receptor complex, and, usually result in fewer systemic side-effects. The potential effects of a pegylated form of IFNλ was assessed in two studies of outpatients and resulted in conflicting data [26,27]. This form of IFN is, to our knowledge, not evaluated in the most severe patients.

Vitamin D

For years, it is known that vitamin D is linked to the innate immune system leading to induction of the defensin β2 and cathelicidin antimicrobial peptides, which can block virus entry into cells as well as suppress viral replication [28,29]. It also increases the phagocytic ability of immune cells and reinforces the physical barrier function of epithelial cells. Vitamin D promotes autophagy, one of the mechanisms by which cells deal with viruses. Finally, vitamin D also modulates the adaptative immune response but research on this led to conflicting results, depending, among others, on the type of disease. Because of these positive effects and the results on the role of vitamin D in respiratory (viral) infections, several experts argued for the evaluation of the use of vitamin D in COVID-19 patients [29,30].

Moreover, lower circulating levels of vitamin D and metabolites is common in critical care and are associated with worse outcomes in critically ill patients, an observation also confirmed in some retrospective studies of COVID-19 patients, showing an inverse relationship between a low level of vitamin D and the incidence of COVID-19 [29,31,32].

More than 90 studies from all over the world are registered on trials.gov. and available results on the potential of vitamin D as adjunctive treatment in COVID-19 were recently reviewed [29–31]. It is uneasy to draw any firm conclusions from the published studies as there was considerable variation in number and type of patients, dosing regimen, duration of treatment, and outcome measures reported. Furthermore, although ICU admission may be an outcome in some studies, ICU patients are most of the time excluded, which makes any generalization of limited interest for ICU patients.

Immune checkpoint inhibitors

Immune checkpoint molecules are negative regulatory receptors expressed on immune cells, acting as a brake for the immune system. However, these molecules may induce T-cell dysfunction in a variety of diseases, such as cancer and infection. Immune checkpoints inhibitors (ICIs) include anti-PD-1, anti-PD ligand-1 (PD-L1), anti-TIM-3, and anti-CTLA-4 antibodies. They activate γδ T cells and mucosal-associated invariant T (MAIT) cells and restore individual cellular-mediated immune-competence.

Interestingly, higher PD-1 expression on T cells characterizes severely affected COVID-19 patients when compared with healthy patients [33]. Furthermore, when patients deteriorated, an enhanced PD-1 and Tim-3 expression on T cells were observed.

Despite ICIs overturned the management of several malignancies and was proposed to treat septic patients [34], a very limited number of studies is recorded on trials.gov. to address the efficacy of ICIs in COVID-19 patients. Among them, a clinical study will evaluate the role of nivolumab in 120 obese patients by assessing the proportion of patients able to be weaned from oxygen at D15 after randomization (NCT04413838). Study completion is expected in June 2021.

PASSIVE IMMUNE BOOSTERS

The treatments described in the following paragraph may not be considered as a booster of patient's own immunity, but rather a way to provide a passive immune protection against a broad range of pathogens [intravenous immunoglobulins (IvIg)] or against a more specific pathogen [hyperimmune globulins (HIGs) and convalescent plasma]. Those treatments may also display some immune

modulation that might have some interest in situations where there is an excessive inflammation.

Intravenous immunoglobulins

Immunoglobulins obtained from healthy donors act through various mechanisms as an immunomodulatory therapy [35]. Case series [36,37] and retrospective studies [38,39] display variable results and prevent from any firm conclusions as there were confounding factors (concomitant treatment, timing of IvIg administration, or dosing) and the number of critical patients looks very limited. Two recent randomized trials, performed in Iran, also display conflicting results. In the first study on 59 patients (30 patients receiving IvIg), mortality rate was significantly lowered (20 versus 48.3%) and IVIg was an independent determinant of mortality in the multivariate regression analysis [40]. In the other trial evaluating IvIg in 52 patients versus 32 patients receiving standard of care, none of the primary outcomes (need for invasive mechanical ventilation and oxygenation, need for admission to ICU, and mortality rate) were positive [41]. At best, a relationship between early timing of treatment and decreased ICU and hospital length of stay is described in survivors.

Hyperimmune globulins

Hyperimmune globulins (HIG) derived from a large pool of individuals with high antibody titers to specific pathogens has been used successfully in the treatment of infections, such as cytomegalovirus and H1N1 influenza [35]. A 'simple' modified caprylic acid method allows for HIG production from pooled convalescent plasma of COVID-19-recovered individuals, leading to a highly purified immunoglobulin G product with more concentrated neutralizing antibody activity [42,43].

One RCT assessing HIG in 50 patients (NCT04521309) is completed but unpublished so far [44], whereas another one with a larger number of patients will be completed in July 2021.]NCT04546581 – The Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) study].

Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) has been proposed to treat the so-called cytokine storm described in the early stages of the Sars-Cov-2 infection, reduce viral burden, clear antifibrinolytic mediators and fibrin degradation products, decrease the levels of injurious free radicals, and viscous components [45]. Case reports [46], case series [47], retrospective studies [48,49], and matched controlled studies [50] provide contrasting results on a potential mortality benefit probably related to the heterogeneous studied populations. Whenever reported, a decreased cytokine level is described and importantly some authors also demonstrate an increased lymphocyte count after TPE [51]. The specific role of TPE and the mechanism of action to explain this improvement, as well as its clinical consequences remain a matter of research. The role of TPE on the improvement of other markers of immunosuppression beyond lymphocyte count certainly warrants further research. Interestingly, Guo *et al.* [52] report on similar results for lymphocytes, by using an artificial blood liver purification system, which consists of modules for plasma replacement, plasma adsorption, and blood/plasma filtration.

Some authors advocate for TPE with convalescent plasma from recovered individuals as the replacement solution [53,54] or with transfusion of convalescent plasma after the TPE procedure [55]. This is hypothesized to improve the benefit of each technique performed alone. The sequential therapy is reported in a case series of 14 patients on mechanical ventilation with apparent good outcomes when compared with the existing literature [55]. The limited number of patients and the absence of control group limit firm conclusions.

Finally, TPE was also used to treat other conditions associated with COVID-19, such as neurological or gastro-intestinal involvement [45].

Convalescent plasma

Plasma from convalescent patients is a form of therapy used as early as 1918 during the 'flu epidemics' and in recent years for SARS, Middle-East respiratory syndrome (MERS), H1N1, and Ebola pandemics [53,56]. In a first report on five critically ill on mechanical ventilation because of severe COVID-19, Shen *et al.* [57] described improved clinical condition and a resolution of ARDS in four out of five patients within 12 days. Since that time, the United States Food and Drug Administration (US FDA) approved the use of convalescent plasma therapy for COVID-19, more than 150 studies from all over the world were recorded on https://clinicaltrials.gov/, and several meta-analysis and systematic reviews have been conducted. Despite the abundant literature, firm conclusions are still a matter of debate. Various designs, setting, titer of antibody [58], timing of treatment [59], and other factors may explain those discordant results. Large recent meta-analysis, including more than 20 000 patients, were unable to demonstrate any significant positive effect

on mortality or other secondary outcomes (length of stay in hospital, need for MV) [60,61].

Although some studies in the particular setting of ICU are still ongoing (NCT04558476) [62], the group of ICU patients randomized in larger trials did not benefit from convalescent plasma [63–66]. In the recently published RECOVERY trial, 617 patients were receiving invasive mechanical ventilation at randomization [66]. Twenty-eight percent were successfully weaned from invasive ventilation in the convalescent plasma group versus 34% in the usual care groups, which confirms that patients undergoing invasive ventilation at time of randomization are unlikely to benefit from convalescent plasma. Two other large convalescent plasma trials were stopped for futility and final publications are awaited: CONCOR-1 (NCT04348656) and REMAP-CAP (NCT02735707).

Monoclonal antibodies

Studies on monoclonal antibodies (mAb) directed against pro-inflammatory molecules (not only IL-6 but also IL-1ra, IL-8, IL-1β, IL-17A, TNFα, etc.) or their receptor are still underway or were recently terminated. In this particular setting, tocilizumab, a recombinant humanized mAb directed against IL-6 receptor inhibiting its signal transduction pathway, certainly is the most studied drug [67]. Although some clinical signs such as fever reportedly improve, results on mortality are somewhat conflicting, some studies demonstrating improved outcome [68], others showing no benefit at all [69].

mAb may also be directed against viral components (for instance, the S protein on the surface of the virus particle). Other mechanisms of action include binding to ACE2 protein (and block the combination of the virus and its receptor) or acting as an ACE2 analog that competitively binds to the viral S protein [70]. Among those mAb, LY-CoV555, an effective antispike neutralizing mAb, received FDA approval in end 2020.

CONCLUSION

Immune therapies in COVID-19 seem of particular interest to treat this condition and its associated well confirmed immune suppression. Among the immune boosting therapies, some positive effects are described for IL-7, thymosin-α, interferons, and vitamin D. Confirmation in large randomized controlled trials are certainly warranted.

The other strategy involve a passive improvement of the immune function through the administration of IvIg or convalescent plasma. Unfortunately, results from large randomized controlled trial (RCT) in this setting were contrasting, and could currently not serve as a recommendation for treating critically ill. The debate remains opened as results from many trials will be available soon.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Sinha P, Matthay MA, Calfee CS. Is a 'cytokine storm' relevant to COVID-19? JAMA Intern Med 2020; 180:1152–1154.
2. Remy KE, Brakenridge SC, Francois B, *et al.* Immunotherapies for COVID-19: lessons learned from sepsis. Lancet Respir Med 2020; 8:946–949.
3. Jamilloux Y, Henry T, Belot A, *et al.* Should we stimulate or suppress immune responses in COVID-19? Cytokine and anticytokine interventions. Autoimmun Rev 2020; 19:102567.
4. Hatmi ZN. A systematic review of systematic reviews on the COVID-19 pandemic. SN Compr Clin Med 2021; 1–18.
5. Remy KE, Mazer M, Striker DA, *et al.* Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. JCI Insight 2020; 5:e140329.
6. Barata TJ, Durum SK, Seddon B. Flip the coin: IL-7 and IL-7R in health and disease. Nat Immunol 2019; 20:1584–1593.
7. François B, Jeannet R, Daix T, *et al.* Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI Insight 2018; 3:e98960.
8. ■ Laterre PF, François B, Collienne C, *et al.* Association of interleukin 7 immunotherapy with lymphocyte counts among patients with severe coronavirus disease 2019 (COVID-19). JAMA Netw Open 2020; 3:e2016485.

First prospective trial assessing IL-7 in 12 critically ill COVID-19 patients compared with 13 matched subjects. Lymphocyte count increased in treated patients.

9. Monneret G, de Marignan D, Coudereau R, *et al.* Immune monitoring of interleukin-7 compassionate use in a critically ill COVID-19 patient. Cell Mol Immunol 2020; 17:1001–1003.
10. Clark IA. Background to new treatments for COVID-19, including its chronicity, through altering elements of the cytokine storm. Rev Med Virol 2020; e2210.
11. Camerini R, Garaci E. Historical review of thymosin α 1 in infectious diseases. Expert Opin Biol Ther 2015; 15(S1):S117–S127.
12. Liu F, Wang HM, Wang T, *et al.* The efficacy of thymosin α1 as immunomodulatory treatment for sepsis: a systematic review of randomized controlled trials. BMC Infect Dis 2016; 16:488.
13. Pei F, Guan X, Wu J. Thymosin alpha 1 treatment for patients with sepsis. Expert Opin Biol Ther 2018; 18(Suppl 1):71–76.
14. Matteucci C, Minutolo A, Balestrieri E, *et al.* Thymosin alpha 1 mitigates cytokine storm in blood cells from coronavirus disease 2019 patients. Open Forum Infect Dis 2020; 8:ofaa588.
15. ■ Liu Y, Pan Y, Hu Z, *et al.* Thymosin alpha 1 reduces the mortality of severe coronavirus disease 2019 by restoration of lymphocytopenia and reversion of exhausted T cells. Clin Infect Dis 2020; 71:2150–2157.

Retrospective study on 36 patients treated with Thymosin-α, compared with a standard-of-care group, showing improvement in T-cell number in lymphopenic severe and critical COVID-19 patients.

16. Costantini C, van de Veerdonk FL, Romani L. Covid-19-associated pulmonary aspergillosis: the other side of the coin. Vaccines (Basel) 2020; 8:713.
17. Garcia-del-Barco D, Risco-Acevedo D, Berlanga-Acosta J, *et al.* Revisiting pleiotropic effects of type i interferons: rationale for its prophylactic and therapeutic use against SARS-CoV-2. Front Immunol 2021; 12:655528.
18. Hadjadj J, Yatim N, Barnabei L, *et al.* Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020; 369:718–724.

19. Venet F, Cour M, Rimmelé T, *et al.,* RICO study group. Longitudinal assessment of IFN-I activity and immune profile in critically ill COVID-19 patients with acute respiratory distress syndrome. Crit Care 2021; 25:140.
20. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. Nat Rev Immunol 2020; 20:397–398.
21. Davoudi-Monfared E, Rahmani H, Khalili H, *et al.* A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19. Antimicrob Agents Chemother 2020; 64:e01061–e1120.
22. ■ Alavi Darazam I, Shokouhi S, Pourhoseingholi MA, *et al.* Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial. Sci Rep 2021; 11:8059.

Prospective randomized trial assessing the effects of type-1 IFN in patients, including critically ill COVID-19 patients. Clinical improvement is reached earlier with treatment.

23. Monk PD, Marsden RJ, Tear VJ, *et al.,* Inhaled Interferon Beta COVID-19 Study Group. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med 2021; 9:196–206.
24. Rahmani H, Davoudi-Monfareda E, Nouriana A, *et al.* Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. Int Immunopharmacol 2020; 88:106903.
25. Bosi E, Bosi C, Rovere Querini P, *et al.* Interferon β-1a (IFNβ-1a) in COVID-19 patients (INTERCOP): study protocol for a randomized controlled trial. Trials 2020; 21:939.
26. Jagannathan P, Andrews JR, Bonilla H, *et al.* Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. Nat Commun 2021; 12:1967.
27. Feld JJ, Kandel C, Biondi MJ, *et al.* Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respir Med 2021; 9:498–510.
28. Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. Nutrients 2018; 10:1656.
29. Bilezikian JP, Bikle D, Hewison M, *et al.* Mechanisms in endocrinology - vitamin D and COVID-19. Eur J Endocrinol 2020; 183:R133–R147.
30. Silberstein M. COVID-19 and IL-6: why vitamin D (probably) helps but tocilizumab might not. Eur J Pharmacol 2021; 15:174031.
31. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health 2020; 13:1373–1380.
32. Charoenngam N, Shirvani A, Holick MF. Vitamin D and its potential benefit for the COVID-19 pandemic. Endocr Pract 2021; 27:484–493.
33. Diao B, Wang C, Tan Y, *et al.* Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020; 11:827.
34. Hotchkiss RS, Colston E, Yende S, *et al.* Immune checkpoint inhibition in sepsis: a phase 1b randomized, placebo-controlled, single ascending dose study of antiprogrammed cell death-ligand 1 antibody (BMS-936559). Crit Care Med 2019; 47:632–642.
35. Nguyen AA, Habiballah SB, Platt CD, *et al.* Immunoglobulins in the treatment of COVID-19 infection: proceed with caution! Clin Immunol 2020; 216:108459.
36. Cao W, Liu X, Bai T, *et al.* High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease. Open Forum Infect Dis 2020; 7:ofaa102.
37. Sheianov MV, Udalov YD, Ochkin SS, *et al.* Pulse therapy with corticosteroids and intravenous immunoglobulin in the management of severe tocilizumab-resistant COVID-19: a report of three clinical cases. Cureus 2020; 12:e9038.
38. Huang C, Fei L, Li W, *et al.* Efficacy evaluation of intravenous immunoglobulin in nonsevere patients with COVID-19: a retrospective cohort study based on propensity score matching. Int J Infect Dis 2021; 105:525–531.
39. Cao W, Liu X, Hong K, *et al.* High-dose intravenous immunoglobulin in severe coronavirus disease 2019: a multicenter retrospective study in China. Front Immunol 2021; 12:627844.
40. Gharebaghi N, Nejadrahim R, Mousavi SJ, *et al.* The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis 2020; 20:786.
41. Tabarsi P, Barati S, Jamaati H, *et al.* Evaluating the effects of intravenous immunoglobulin (IVIg) on the management of severe COVID-19 cases: a randomized controlled trial. Int Immunopharmacol 2021; 90:107205.
42. Ali S, Uddin SM, Ali A, *et al.* Production of hyperimmune anti-SARS-CoV-2 intravenous immunoglobulin from pooled COVID-19 convalescent plasma. Immunotherapy 2021; 13:397–407.
43. Vandeberg P, Cruz M, Diez JM, *et al.* Brief report: Production of anti-SARS-CoV-2 hyperimmune globulin from convalescent plasma. Transfusion 2021; 61:1705–1709.
44. Ali S, Luxmi S, Anjum F, *et al.* Hyperimmune anti-COVID-19 IVIG (C-IVIG) therapy for passive immunization of severe and critically ill COVID-19 patients: a structured summary of a study protocol for a randomised controlled trial. Trials 2020; 21:905.
45. Lu W, Kelley W, Fang DC, *et al.* The use of therapeutic plasma exchange as adjunctive therapy in the treatment of coronavirus disease 2019: a critical appraisal of the current evidence. J Clin Apher 2021; 36:483–491.
46. Keith P, Day M, Choe C, *et al.* The successful use of therapeutic plasma exchange for severe COVID-19 acute respiratory distress syndrome with multiple organ failure. SAGE Open Med Case Rep 2020; 8:. 2050313X20933473.
47. Khamis F, Al-Zakwani I, al Hashmi S, *et al.* Therapeutic plasma exchange in adults with severe COVID-19 infection. Int J Infect Dis 2020; 99:214–218.
48. Gucyetmez B, Atalan HK, Sertdemir I, *et al.,* COVID-19 Study Group. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. Crit Care 2020; 24:492.
49. Keith PD, Wells AH, Hodges J, *et al.* The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: a single-center experience. Crit Care 2020; 24:518.
50. Gluck WL, Callahan SP, Brevetta RA, *et al.* Efficacy of therapeutic plasma exchange in the treatment of penn class 3 and 4 cytokine release syndrome complicating COVID-19. Respir Med 2020; 175:106188.
51. Faqihi F, Alharthy A, Abdulaziz S, *et al.* Therapeutic plasma exchange in patients with life-threatening COVID-19: a randomised controlled clinical trial. Int J Antimicrob Agents 2021; 57:106334.
52. Guo J, Xia H, Wang S, *et al.* The artificial-liver blood-purification system can effectively improve hypercytokinemia for COVID-19. Front Immunol 2020; 11:586073.
53. Varghese J, Subramanian P, Jayanthi V. Therapeutic plasma exchange using convalescent plasma replacement therapy in severe COVID-19 infections: a potential therapeutic option. EMJ Innov 2021; 5:78–81.
54. Kesici S, Yavuz S, Bayrakci B. Get rid of the bad first: therapeutic plasma exchange with convalescent plasma for severe COVID-19. Proc Natl Acad Sci U S A 2020; 117:12526–12527.
55. Jaiswal V, Nasa P, Raouf M, *et al.* Therapeutic plasma exchange followed by convalescent plasma transfusion in critical COVID-19 - an exploratory study. Int J Infect Dis 2020; 102:332–334.
56. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020; 20:398–400.
57. Shen C, Wang Z, Zhao F, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020; 323:1582–1589.
58. Joyner MJ, Carter RE, Senefeld JW, *et al.* Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021; 384:1015–1027.
59. Libster R, Pérez Marc G, Wappner D, *et al.,* Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med 2021; 384:610–618.
60. Janiaud P, Axfors C, Schmitt AM, *et al.* Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. JAMA 2021; 325:1185–1195.
61. Chai KL, Valk SJ, Piechotta V, *et al.* Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev 2020; 10:CD013600.
62. Misset B, Hoste E, Donneau AF, *et al.* A multicenter randomized trial to assess the efficacy of CONvalescent plasma therapy in patients with Invasive COVID-19 and acute respiratory failure treated with mechanical ventilation: the CONFIDENT trial protocol. BMC Pulm Med 2020; 20:317.
63. Klapholz M, Pentakota SR, Zertuche JP, *et al.* Matched Cohort Study of Convalescent COVID-19 Plasma Treatment in severely or life threateningly ill Covid-19 patients. Open Forum Infect Dis 2021; 8:ofab001.
64. Li L, Zhang W, Hu Y, *et al.* Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020; 324:460–470.
65. Simonovich VA, Burgos Pratx LD, Scibona P, *et al.,* PlasmAr Study Group. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med 2021; 384:619–629.
66. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021; 397:2049–2059.
67. Patel S, Saxena B, Mehta P. Recent updates in the clinical trials of therapeutic monoclonal antibodies targeting cytokine storm for the management of COVID-19. Heliyon 2021; 7:e06158.
68. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; 397:1637–1645.
69. Canziani LM, Trovati S, Brunetta E, *et al.,* Humanitas and Gavazzeni/Castelli COVID-19 Task Forces. Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: a retrospective case-control survival analysis of 128 patients. J Autoimmun 2020; 114:102511.
70. Yuan C, Li R, Liu G, Pan Y. Potential of immune-related therapy in COVID-19. Front Pharmacol 2021; 11:609212.