Host Modifiers and Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Several immune therapies directed at modifying the course of COVID-19 are currently under investigation or are used off-label. These agents may target the virus (e.g., convalescent plasma) or modulate the immune response (e.g., interleukin-1 [IL-1] or interleukin-6 [IL-6] inhibitors).

For more information on host modifiers and immunotherapy under evaluation for COVID-19, see Tables 3a and 3b.

Convalescent Plasma and Specific Immune Globulins

Recommendation:

- There are insufficient data to recommend either for or against the use of convalescent plasma or hyperimmune immunoglobulin for the treatment of COVID-19 **(AIII).**

Rationale for Recommendation:

Although convalescent plasma and hyperimmune immunoglobulin have been used for other viral infections, sufficient clinical data are lacking for COVID-19, and theoretical risks exist of antibody-dependent enhancement of infection and transfusion-associated acute lung injury (TRALI).

Rationale for Use in Patients with COVID-19:

Plasma donated from individuals who have recovered from COVID-19, which includes antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may help suppress the virus and may modify the inflammatory response.[1-10] SARS-CoV-2 intravenous immune globulin (IVIG) is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19.

Clinical Experience in Patients with Viral Infections:

- Data supporting the use of convalescent plasma for COVID-19 and severe acute respiratory syndrome (SARS) are limited to case reports and case series. There are no clinical data on the use of specific immune globulin or hyperimmune immunoglobulin in COVID-19, SARS, or Middle East respiratory syndrome (MERS).
- The use of convalescent plasma has been evaluated in other viral diseases, with some evidence of potential benefit. No such products are currently licensed by Food and Drug Administration (FDA).
- Several specific immune globulin products are licensed for preventing post-transplant cytomegalovirus (CMV) disease (Cytogam) and post-exposure prophylaxis of varicella in high-risk individuals (VariZig).
- Risks associated with plasma transfusion include antibody-mediated enhancement of infection, TRALI, transfusion-associated circulatory overload, and allergic transfusion reactions.[11] Rare complications include transmission of infectious diseases and red cell alloimmunization.
- Clinical trials to evaluate both convalescent plasma and SARS-CoV-2 IVIG for the treatment of COVID-19 are in development.
- FDA has provided guidance for the use of COVID-19 convalescent plasma under Emergency Investigational New Drug Application.
- FDA has approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National

COVID-19 Convalescent Plasma Project website for more information. People who have fully recovered from COVID-19 for at least two weeks and are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the American Red Cross website.

Considerations in Pregnancy:

- Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children:

- Hyperimmune globulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus (RSV), and CMV; efficacy data for other respiratory viruses is limited.
- The efficacy and/or adverse effects (AEs) associated with administration of convalescent plasma have not been well established.

Interleukin-1 and Interleukin-6 Inhibitors and Other Immunomodulators

The cytokine profiles of serum from some patients with moderate to severe COVID-19 overlap with those seen in macrophage activation syndrome (MAS) and secondary hemophagocytic lymphohistiocytosis (sHLH).[12] MAS is characterized by hyperinflammation and manifests as fever, elevated ferritin levels, and pulmonary involvement, with a spectrum of presentation that includes sHLH.[13] Viruses are known triggers of MAS/sHLH, and high ferritin levels are associated with both MAS and mortality in patients with COVID-19.[14,15] Endogenous IL-1, a proinflammatory cytokine, potently induces IL-6 in monocytes and macrophages and is elevated in patients with COVID-19, MAS, and other conditions, such as severe chimeric antigen receptor T-cell (CAR-T) mediated cytokine release syndrome (CRS).[16] The Janus kinase (JAK) family of enzymes regulate signal transduction in immune cells, and JAK inhibitors play a major role in inhibiting and blocking cytokine release. IL-6 and IL-1 blockades and JAK inhibition, both of which have been proposed as an approach to treat the systemic inflammation associated with severe COVID-19 illness,[17] are reviewed below.

IL-1 Inhibitors (e.g., Anakinra)

Recommendation:

- There are insufficient data to recommend either for or against the use of **IL-1 inhibitors**, such as **anakinra**, for the treatment of COVID-19 **(AIII)**.

Rationale for Recommendation:

There are no data from clinical trials on the use of IL-6 antagonist in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist (rhIL-1ra). It is approved to treat a variety of inflammatory conditions that range from RA to familial Mediterranean fever and is also used off-label for severe CAR-T-mediated CRS and MAS/sHLH.

Proposed Mechanism of Action and Rationale for Use:

Endogenous IL-1 is elevated in COVID-19 and other conditions, such as severe CAR-T-mediated CRS.

Clinical Data for COVID-19:

There are no published studies to date on the use of anakinra in COVID-19 infection or for other novel coronavirus infections (i.e., SARS, MERS).

Clinical Trials:

An open-label randomized trial underway in Italy is comparing IV-administered anakinra to IV-administered emapalumab (an interferon gamma [IFNγ]–blocking antibody) for the treatment of COVID-19.

Adverse Effects and Monitoring:

Anakinra was not associated with any significant safety concerns in trials of sepsis.[18-20] Increased rates of infection were reported with prolonged use in combination with tumor necrosis factor-alfa blockade, but not with short-term use.[21]

Considerations in Pregnancy:

Limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.[22]

Considerations in Children:

- Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS.
- Pediatric data for use of anakinra in acute respiratory distress syndrome (ARDS)/sepsis are limited.

Drug Availability:

Procurement of anakinra may be a challenge at some hospitals in the United States Anakinra is approved only in a subcutaneous (SQ) formulation.

IL-6 Inhibitors (Sarilumab, Siltuximab, Tocilizumab)

Recommendation:

- There are insufficient data to recommend either for or against the use of **IL-6 inhibitors** (e.g., **sarilumab, siltuximab, or tocilizumab**) for the treatment of COVID-19 **(AIII)**.

Rationale for Recommendation:

There are no data from clinical trials on the use of IL-6 inhibitors in patients with COVID-19.

Rationale for Use of IL-6 Inhibition in COVID-19:

- IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts.
- Infection by the related SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.[23] Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with SARS-CoV-2 infection.
- COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release as indicated by elevated blood levels of IL-6, C-reactive protein, D-dimer, and ferritin, but typically not procalcitonin.[15,24,25]

Sarilumab

Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is FDA-approved for use in patients with RA. It is dosed subcutaneously (SQ) and is not approved for CRS. A placebo-controlled clinical trial is evaluating the use of an IV formulation administered as a single dose for COVID-19.

Clinical Data in COVID-19:

There are currently no data from randomized clinical trials or large observational cohorts describing the efficacy of sarilumab among patients with COVID-19.

Potential Adverse Effects and Monitoring:

Primary lab abnormalities reported with sarilumab treatment are transient/reversible elevations in liver enzymes that appear dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., tuberculosis [TB], other bacterial pathogens) have been reported only in the context of long-term use of sarilumab.

Considerations in Pregnancy:

There are insufficient data to determine if there is a drug-associated risk for major birth defects or miscarriage.

Drug Availability:

The SQ formulation is not approved for CRS. The IV formulation is not FDA-approved but is being studied in a clinical trial of hospitalized patients with COVID-19. A list of current clinical trials is available at: *ClinicalTrials.gov*.

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 that is FDA-approved for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R and thereby inhibits IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19:

There are limited data describing the efficacy of siltuximab in patients with COVID-19.[26] There are also no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., SARS, MERS).

Potential Adverse Effects and Monitoring:

The primary AEs reported for siltuximab have been related to rash. Additional AEs such as serious bacterial infections have been reported only in the context of long-term dosing of siltuximab once every three weeks.

Considerations in Pregnancy:

There are insufficient data to determine if there is a drug-associated risk for major birth defects or miscarriage.

Drug Availability:

It may be a challenge to procure siltuximab at some hospitals in the United States.

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is FDA-approved for use in patients with rheumatologic disorders and CRS-induced by CAR T-cell therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.[27]

Clinical Data for COVID-19:

- There are no data from randomized clinical trials or large observational cohort studies describing the efficacy of tocilizumab in patients with COVID-19.
- There are anecdotal reports of improved oxygenation in patients with COVID-19, systemic inflammation, and hypoxic respiratory failure who received tocilizumab.[28]

Potential Adverse Effects and Monitoring:

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzymes that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs such as risk for serious infections (e.g., TB, other bacterial pathogens) have been reported only in the context of continuous dosing of tocilizumab.

Considerations in Pregnancy:

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects and miscarriage. Monoclonal antibodies are actively transported across the placenta in the third trimester and may affect immune responses *in utero* in the exposed infant.

Considerations in Children:

Tocilizumab is frequently used in CRS following CAR T-cell therapy,[29] and occasionally for MAS in children.[30] Pediatric data for its use in ARDS/sepsis are limited.

Drug Availability:

Procurement of IV tocilizumab may be a challenge at some hospitals in the United States.

Clinical Trials:

See *ClinicalTrials.gov* for ongoing trials of tocilizumab for the treatment of COVID-19.

Other Immunomodulators

Interferons (Alpha, Beta)

Recommendation:

- The Panel **recommends against** the use of **interferons** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Rationale for Recommendation:

Considered together, the absence of benefit when interferons were used in other coronavirus infections (i.e., MERS, SARS), the lack of clinical trial results in COVID-19, and the significant toxicities of interferons outweigh the potential for benefit.

Rationale for Use:

Interferons, a family of cytokines with antiviral properties, have been suggested as a potential treatment of COVID-19 for their *in vitro* and *in vivo* antiviral properties.

Clinical Data in COVID-19:

- Interferon-beta used alone and in combination with ribavirin in SARS and MERS has failed to show a significant positive effect on clinical outcomes.[31-35]
- In a retrospective observational analysis of 350 critically ill patients with MERS[32] from 14 hospitals in Saudi Arabia, mortality rates were higher among patients who received ribavirin and interferon (-beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.
- A randomized clinical trial that included 301 patients with ARDS[36] found that, compared to placebo, IV interferon beta-1a had no benefit as measured by ventilator-free days over a 28-day period (median, 10.0 vs 8.5 days) or mortality (26.4% vs 23.0%).
- INF-alfa-1b, which is not available in the United States, has been used in patients with COVID-19 in China, but it has been primarily used by atomization inhalation, and the clinical data have not yet been presented.

Adverse Effects and Monitoring:

The most frequent AEs of interferon-alfa include flu-like symptoms, hematological toxicities (cytopenias) including elevated transaminases, nausea, fatigue, weight loss, and psychiatric problems (depression and suicidal ideation). Interferon-beta is better tolerated.

Drug-Drug Interactions:

The most serious interactions with interferons are the potential for added toxicity with other immunomodulators and chemotherapeutic agents.

Considerations in Pregnancy:

Data from several large pregnancy registries did not demonstrate an association between exposure to interferon beta-1b pre-conception or during pregnancy and an increase risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly) and did not influence birth weight, height, or head circumference.

Considerations in Children:

There are limited data on the use of interferons for the treatment of respiratory viral infections in children.

Janus Kinase Inhibitors (e.g., Baricitinib)

Recommendation:

- The Panel **recommends against** the use of Janus kinase **(JAK) inhibitors** (e.g., **baricitinib**) for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Rationale for Recommendation:

At present, the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit.

Baricitinib is an oral JAK inhibitor that works by inhibiting the JAK-signal transducer and activator of transcription (STAT) pathway. Baricitinib is FDA-approved to treat RA and can ameliorate the chronic inflammation seen in interferonopathies.[37-39]

Rationale for Use in COVID-19:

Baricitinib is a potent anti-inflammatory with activity against interferon-associated inflammation. It has also been postulated to have an antiviral effect. A related drug, ibrutinib, has been shown to decrease lung inflammation in a mouse model of influenza.[40,41]

Clinical Data for COVID-19:

None reported to date.

Adverse Effects:

Side effects with prolonged use include upper respiratory infections (>10% of patients), increased low-density lipoproteins, herpesvirus infections, increased liver function test levels, and thrombocytosis.

Considerations in Pregnancy:

- In animal studies of embryo-fetal development, there was increased embryolethality in some species given baricitinib at very high doses, well above the recommended dose for humans.[42]
- The limited human data on the use of baricitinib are insufficient to evaluate the drug-associated risk for major birth defects or miscarriage.[42]

Corticosteroids

The role of corticosteroids as concomitant therapy in persons with COVID-19 are discussed in Considerations for Certain Concomitant Medications in Patients with COVID-19.

References

1. Chun S, Chung CR, Ha YE, et al. Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. *Ann Lab Med*. 2016;36(4):393-395. Available at:https://www.ncbi.nlm.nih.gov/pubmed/27139619.
2. Burnouf T, Radosevich M. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J.* 2003;9(4):309; author reply 310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12904626.
3. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15616839.
4. Kong L. Severe acute respiratory syndrome (SARS). *Transfus Apher Sci.* 2003;29(1):101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12952008.
5. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25030060.
6. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect*. 2004;10(7):676-678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15214887.
7. Yeh KM, Chiueh TS, Siu LK, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *J Antimicrob Chemother*. 2005;56(5):919-922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16183666.
8. Duan K, Liu B, Li C, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.
9. Beigel JH, Tebas P, Elie-Turenne MC, et al. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respir Med*. 2017;5(6):500-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28522352.

10. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32219428.
11. Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. *Transfusion*. 2012;52(1):160-165. Available at:https://www.ncbi.nlm.nih.gov/pubmed/21762464.
12. Pedersen SF, Ho Y. SARS-CoV-2: A storm is raging. *The Journal of Clinical Investigation*. 2020. [In press]. Available at: https://www.jci.org/articles/view/137647.
13. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516. Available at:https://www.ncbi.nlm.nih.gov/pubmed/24290661.
14. Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest*. 2016;149(5):1294-1301. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26836913.
15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at:https://www.ncbi.nlm.nih.gov/pubmed/31986264.
16. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275-281. Available at:https://www.ncbi.nlm.nih.gov/pubmed/26584195.
17. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. Available at:https://www.ncbi.nlm.nih.gov/pubmed/32192578.
18. Fisher CJ, Jr., Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843. Available at:https://www.ncbi.nlm.nih.gov/pubmed/8196140.
19. Fisher CJ, Jr., Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med*. 1994;22(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8124953.
20. Opal SM, Fisher CJ, Jr., Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med.* 1997;25(7):1115-1124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9233735.
21. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24 Suppl 2:S21-S40. Available at:https://www.ncbi.nlm.nih.gov/pubmed/29447987.
22. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. *Rheumatology (Oxford)*. 2016;55(9):1698-1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26750125.
23. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19004938.
24. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at:https://www.ncbi.nlm.nih.gov/pubmed/32171076.
25. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis. 2020*. Available

at:https://www.ncbi.nlm.nih.gov/pubmed/32176772.

26. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020. Available at:https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1.
27. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T Cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at:https://www.ncbi.nlm.nih.gov/pubmed/29622697.
28. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *ChinaXiv*. 2020. Available at:http://www.chinaxiv.org/user/download.htm?id=30387.
29. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. *Blood*. 2019;134(24):2149-2158. Available at:https://www.ncbi.nlm.nih.gov/pubmed/31697826.
30. Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol*. 2015;42(4):712-722. Available at:https://www.ncbi.nlm.nih.gov/pubmed/25684767.
31. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis*. 2014;20:42-46. Available at:https://www.ncbi.nlm.nih.gov/pubmed/24406736.
32. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31925415.
33. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. Available at:https://www.ncbi.nlm.nih.gov/pubmed/14985565.
34. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at:https://www.ncbi.nlm.nih.gov/pubmed/25278221.
35. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alf2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at:https://www.ncbi.nlm.nih.gov/pubmed/25900158.
36. Ranieri VM, Pettila V, Karvonen MK, et al. Effect of intravenous interferon beta-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2020. Available at:https://www.ncbi.nlm.nih.gov/pubmed/32065831.
37. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252. Available at:https://www.ncbi.nlm.nih.gov/pubmed/27028914.
38. Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol*. 2019;46(1):7-18. Available at:https://www.ncbi.nlm.nih.gov/pubmed/30219772.
39. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95. Available at:https://www.ncbi.nlm.nih.gov/pubmed/27689735.
40. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at:https://www.ncbi.nlm.nih.gov/pubmed/32032529.
41. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. Available at:https://www.ncbi.nlm.nih.gov/pubmed/32113509.
42. OLUMIANT (baricitinib) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf. Accessed: April 8, 2020.