EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2022.2035360

Taylor & Francis
Taylor & Francis Group

REVIEW

Current and emerging immunomodulators for treatment of SARS-CoV2 infection (COVID-19)

Matthew W. McCarthy

Weill Cornell Medicine, Division of General Internal Medicine, New York, NY, USA

ABSTRACT

Introduction: SARS-CoV-2, the virus that causes COVID-19, elicits a variety of host responses ranging from asymptomatic or mild illness in most people, to severe disease and critical illness in a subset of patients with systemic inflammation and hypoxemic respiratory failure.

Areas Covered: Heterogeneous clinical presentations are often driven by disparate responses of the host immune system, with severe disease associated with aberrant interferon signaling or cytokine storm syndrome. This manuscript examines current therapeutic approaches, including the use of immunomodulators such as corticosteroids, interleukin inhibitors, kinase inhibitors, fluvoxamine, and ivermectin, and also explores the ways that these therapies and others may be used to treat COVID-19 in the future.

Expert opinion: Modulation of the immune response has become a mainstay of treatment of COVID-19, although the optimal mechanism has not yet been defined and there is considerable controversy regarding clinical management. As time progresses, the therapeutic approach to COVID-19 will undoubtedly change, particularly as we learn more about the pathophysiology of SARS-CoV-2 infection.

ARTICLE HISTORY
Received 3 November 2021
Accepted 25 January 2022

KEYWORDS
COVID-19; immunomodulator; SARS-CoV-2; inflammation; cytokine storm

1. Introduction

During the first wave of the coronavirus pandemic, corticosteroids such as dexamethasone and prednisone were used sparingly in the treatment of COVID-19 owing to the suggestion that these drugs could enhance both viral shedding and progression of disease of other coronaviruses such as SARS-COV and Middle East Respiratory Syndrome (MERS) [1,2]. The trajectory of the COVID-19 pandemic changed in the summer of 2020, however, with the publication of the manuscript, 'Dexamethasone in Hospitalized Patients with COVID-19' from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial, a large-scale, randomized trial of repurposed drugs [3].

In this landmark study, 2104 volunteers hospitalized with COVID-19 received dexamethasone while 4321 subjects received usual care [3]. In total, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization. A crucial finding of the study was that the incidence of death was lower in the dexamethasone group than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%). However, dexamethasone demonstrated no statistically significant benefit among those without hypoxia.

This study revolutionized the therapeutic approach to COVID-19 [4–6]. The finding that an inexpensive, widely available immunomodulator resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone ignited a hunt for other drugs that might work though similar mechanisms [7–9].

Rather than attempting to discover novel therapeutics, however, many clinical investigators elected to study existing drugs with known safety profiles [7]. This was a strategic decision necessitated by the devastating wrought by the global pandemic [10,11]. While basic scientists attempted to tease out the immunological underpinnings of severe COVID-19, and the role that inflammation may play in the emergence of viral resistance, clinical trialists began experimenting with a variety of immunomodulators, which will be discussed below [12,13].

2. Immunomodulators for hospitalized patients

2.1. Interleukin-6 inhibitors

SARS-CoV-2 infection produces a variety of responses in humans [14–17]. Those who require hospitalization are often found to have evidence of systemic inflammation associated with elevated blood levels of interleukin-6 (IL-6) [18]. It has been suggested that reducing IL-6 levels may ameliorate illness with either of two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g. tocilizumab and sarilumab) and anti-IL-6 mAbs (i.e. siltuximab) [19–21]. The data, however, have been mixed for hospitalized patients [22].

CONTACT Matthew W. McCarthy mwm9004@med.cornell.edu Weill Cornell Medicine, Division of General Internal Medicine, 525 East 68th Street, New York, NY 10065, USA

Article highlights

*Severe COVID-19 is associated with misfiring of the human immune system.

*Systemic corticosteroids have become a mainstay of treatment for hospitalized patients with COVID-19 who require supplemental oxygen.

*Tocilizumab is an interleukin-6 receptor antagonist approved for patients with rheumatologic disorders and has improved outcomes in a subset of hospitalized COVID-19 patients with signs of systemic inflammation and increasing oxygen requirements.

*Janus kinase (JAK) inhibitors interfere with cell signaling and signal transduction that leads to immune activation and have improved outcomes in some hypoxic hospitalized patients with COVID-19

*The antidepressant fluvoxamine has shown promise for outpatients newly diagnosed with COVID-19

Tocilizumab is a recombinant humanized anti-IL-6 receptor mAb approved for patients with rheumatologic disorders such as giant cell arteritis and rheumatoid arthritis as well as cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy [23]. Given the finding that many patients with severe COVID-19 demonstrate signs of cytokine release syndrome, there has been intense interest in using this drug in patients hospitalized with COVID-19 [24].

A single-center propensity-score matched cohort study was performed evaluating consecutive hospitalized COVID-19 patients in 2020 [25]. Subjects were stratified according to the receipt of tocilizumab for cytokine storm and matched to controls using propensity scores; 274 patients screened and 132 were included in the matched dataset (tocilizumab = 66; no tocilizumab = 66). There were 18 deaths (27.3%) in the tocilizumab group and 18 deaths (27.3%) in the no tocilizumab group (p = 1.00). This small study did not support the use of tocilizumab for the management of cytokine storm in patients with COVID-19. Nevertheless, interleukin antagonist research continued [26,27].

The RECOVERY study subsequently evaluated tocilizumab in patients with hospitalized with COVID-19 randomized, controlled, open-label trial [28]. Volunteers with hypoxia and evidence of systemic inflammation (c-reactive protein P ≥ 75 mg/L) were randomized to standard or care with or without tocilizumab. A total of 4116 volunteers enrolled, including 3385 (82%) subjects receiving corticosteroids; 621 (31%) of the 2022 patients given tocilizumab and 729 (35%) of the 2094 patients randomized to standard of care died within 28 days (p = 0.0028). Those receiving tocilizumab were more likely to be discharged from hospital within 28 days (p < 0 · 0001). The RECOVERY study clearly demonstrated in a large-scale, randomized study that tocilizumab improved survival and other clinical outcomes in patients hypoxic patients with COVID-19 and signs of systemic inflammation [28].

Tocilizumab and the IL-6 antagonist sarilumab were evaluated in an international, multifactorial, adaptive platform trial, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) [29]. Adults with COVID-19 requiring intensive care unit (ICU) care were randomly assigned to receive tocilizumab, sarilumab, or standard care. A total of 353 patients were given tocilizumab, 48 received sarilumab, and 402 were in the control group. The median number of organ support-free days was 10 in the tocilizumab group, 11 in the sarilumab group, and 0 in the control group. The 90-day mortality rate revealed improved survival for those receiving either of the two IL-6 antagonists. While small studies showed minimal benefit (or, in some cases, harm), these large, randomized studies showed a clear benefit for a subset of patients [30,31].

Based on these studies, IL-6 inhibitors (tocilizumab and sarilumab) are now used by many clinical in hospitalized COVID-19 patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation in conjunction with dexamethasone. Although the optimal patient population has not yet been defined, there appears to be a role for IL-6 inhibition in patients with a rapidly-escalating oxygen requirement and elevated inflammatory markers (C-reactive protein >7.5) if given within the first three days of hospitalization. There may also be a role for anti-IL-6 mAb therapy (i.e. siltuximab) but more data is necessary and for now, the drug should only be used within the confines of a clinical trial [19–21]. This work has shown the clear benefits of immunomodulation, and expanded the search for other drugs with anti-inflammatory properties. There is also considerable interest in IL-1 inhibition with the rheumatologic drug anakinra. However, the optimal COVID-19 patient population has not yet been defined.

2.2. Janus kinase inhibitors

Janus kinase (JAK) inhibitors interfere with phosphorylation of signaling molecules and activator of transcription (STAT) proteins that are implicated in cell signaling, growth, and survival [31]. JAK inhibitors, such as baricitinib and tofacitinib, have been suggested as treatments for COVID-19 because they can halt signal transduction that leads to immune activation and systemic inflammation [32,33].

Baricitinib was evaluated in a double-blind, randomized, placebo-controlled trial, Adaptive Covid-19 Treatment Trial (ACTT-2) [34]. The drug was administered with remdesivir to adults hospitalized with Covid-19. In total, 515 received combination treatment and 518 were in the control group. Patients receiving baricitinib had a median time to recovery of 7 days as compared with 8 days for those in the control group (P = 0.03), and 30% greater odds of symptomatic improvement at day 15 (odds ratio 1.3). Importantly, subjects receiving supplemental oxygen had a time to recovery of 10 days with combination treatment and 18 days with control and the four-week mortality was 5.1% in the combination group and 7.8% in the control group with fewer serious adverse events.

In another trial, the Study of Tofacitinib in Hospitalized Patients with Covid-19 Pneumonia (STOP-COVID), the JAK inhibitor tofacitinib was compared with placebo in hospitalized patients with COVID-19 [35]. A total of 289 volunteers underwent randomization; the incidence of death or respiratory failure after four weeks was 18.1% in the tofacitinib group

and 29.0% in the placebo group (P = 0.04). Death from any cause occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group after four weeks. The key finding from this work, in which 89.3% of patients also received dexamethasone, was that tofacitinib led to a lower risk of death or respiratory failure than placebo after four weeks [35].

Guidelines from the United States National Institutes of Health (NIH) now recommend the use of the JAK inhibitor baricitinib or the IL-6 antagonist tocilizumab in conjunction with dexamethasone plus the antiviral remdesivir for recently hospitalized patients with COVID-19 in the setting of rapidly increasing oxygen needs and systemic inflammation. If these drugs are not available, the IL-6 inhibitor sarilumab may be used in place of tocilizumab and the JAK inhibitor tofacitinib may be used instead of baricitinib [18]. The successful use of these immunomodulators in hospitalized patients has led some investigators to believe that a similar approach is warranted for outpatients with COVID-19, especially those at high risk for hospitalization.

3. Immunomodulators for outpatients

There are no FDA-approve treatments for outpatients with newly diagnosed COVID-19. Monoclonal antibody therapy has demonstrated notable safety and efficacy for those at high-risk of hospitalization, but therapeutic options for low- and moderate-risk outpatients are lacking [36]. Moreover, the resources associated with antibody infusion limit its use in many locations. A number of antiviral treatments are under investigation, but there are no oral antiviral treatment options currently available to outpatients. In this setting of limited therapeutics, immunomodulators have emerged as a promising treatment option.

3.1. Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that was approved by the United States Food and Drug Administration (FDA) in 1994 for the treatment of obsessive-compulsive disorder and is now used to treat a variety of psychiatric conditions [37–39]. Beyond its neuropsychiatric effects, fluvoxamine has been noted to have anti-inflammatory properties that may benefit patients with newly-diagnosed COVID-19 [40].

In vitro experiments demonstrated that the drug limits uptake of the neurotransmitter 5-hydroxytryptamine (5-HT), also known as serotonin, by brain synaptosomes [41]. The therapeutic applications for fluvoxamine expanded, however, after it was observed that there is a close connection between the central nervous system and the human immune system and that depression might be related to aberrant immune activation. Down-regulation of inflammatory genes, such as intercellular adhesion molecule ($ICAM_1$), vascular cell adhesion molecule ($VCAM_1$), cyclooxygenases2 (COX_2), and inducible nitric oxide synthase (iNOS) supported a therapeutic role for fluvoxamine as an anti-inflammatory medication [42,43]. Fluvoxamine has also been shown to interact with the endoplasmic reticulum sigma-1 receptor (S1R) chaperone protein; fluvoxamine has a high affinity for S1R, which in turn dampens the immune response [44,45].

Based on these findings, a double blind, randomized trial was performed to determine whether fluvoxamine prevents outpatient clinical deterioration and decreases the severity of disease [46]. One hundred fifty-two non-hospitalized adults with COVID-19 symptom onset within 7 days and oxygen saturation of 92% or greater were enrolled; participants were randomized to fluvoxamine (n = 80) or placebo (n = 72) for 15 days. Clinical deterioration occurred in none of the 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (P = .009).

Another prospective cohort study of 65 outpatient volunteers recently diagnosed with SARS-CoV-2 who received fluvoxamine were compared to 48 who declined the drug. Of the patients who received fluvoxamine, none were ultimately hospitalized; of those who declined (and received observation alone), six were eventually hospitalized (12.5%) [47]. This study was not randomized, but it provides additional support for further study of this drug in outpatients with COVID-19.

Perhaps most encouragingly, however, was the finding that fluvoxamine (100 mg twice daily for 10 days) reduced need for hospitalization defined as retention in a COVID-19 emergency setting or transfer to a hospital among high-risk outpatients in Brazil with newly diagnosed COVID-19 [48]. The proportion of patients observed in a COVID-19 emergency setting for more than six hours or transferred to a hospital due was lower for the fluvoxamine group compared with placebo (11% vs 16%). The finding established fluvoxamine, an inexpensive and widely available oral medication, as an important therapeutic option in the armamentarium against COVID-19.

3.2. Fluticasone

The glucocorticoid fluticasone is a potent immunomodulator, altering inflammatory pathways involving cytokines, leukotrienes, eicosanoids, and histamines in mast cells, macrophages, eosinophils, and lymphocytes [49–51]. When inhaled, fluticasone decreases local and systemic production of a variety of anti-inflammatory compounds, such as nitric oxide synthase, annexin-1, SLP1, GILZ, IL-6, MOP-1 [52,53]. Fluticasone also increases apoptosis in white blood cells, including lymphocytes, eosinophils, mast cells, and macrophages, all of which have been implicated in the pathophysiology of COVID-19 [49,50,54]. Other inhaled corticosteroids, such as budesonide, exert similar effects and may also play a role in the treatment of COVID-19.

Although randomized trial data are lacking, inhaled fluticasone appears to be a promising therapeutic option based on findings of other corticosteroids (dexamethasone), which has been shown to serve as an important immunomodulator in hospitalized patients with COVID-19. Further studies are necessary, however, in order to clarify the optimal dose, duration, and method of administration for outpatients.

3.3. Ivermectin

Ivermectin has been in clinical use since 1981 and appears on the World Health Organization's List of Essential Medicines for treating a range of parasitic infections in humans, including river blindness and lymphatic filariasis [55]. The drug has also been noted to have both antiviral and immunomodulatory properties, which make it appealing as a therapeutic option for COVID-19 [31,32]. Ivermectin has also received substantial media attention because of its use in veterinary medicine.

Ivermectin reduces the production of tumor necrosis factor (TNF)-alpha, IL-1 and IL-6 and numerous non-randomized, underpowered studies have demonstrated clinical efficacy in small studies [56]. However, the optimal dose, duration, and treatment population have not yet been identified and further studies are ongoing and it is not currently recommended as a treatment for COVID-19.

4. Expert opinion

COVID-19 disease has been broadly divided into an initial viral phase followed by an inflammatory phase. A number of immunomodulators have been investigated to address the inflammatory phase, and these drugs can be further separated into those used for outpatients and those used for hospitalized patients. In addition to the drugs mentioned above, a number of other immunomodulators are under investigation for hospitalized patients. On 17 April 2020 the NIH announced the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising therapeutics and vaccines [9]. ACTIV-1 is a master protocol designed to evaluate multiple immunodulators for moderately or severely ill patients infected with SARS-CoV-2.

ACTIV-1 has included three drugs thus far: abatacept, infliximab, and cenicriviroc. (Cenicriviroc has been removed from the study due to futility and will not be discussed further) [7]. Abatacept, a selective costimulation modulator, inhibits T cell activation by binding to cluster of differentiation 80 (CD80) and CD86, thereby blocking interaction with CD28 and full activation of T lymphocytes [57]. The rationale for studying abatacept is grounded in the working model of the coronavirus life cycle, which suggests that the virus initially infects and replicates in human epithelial cells in the nasopharynx. T cells are recruited to this site and activated, releasing interferon-gamma (IFNγ), which activates alveolar macrophages, creating an inflammatory signaling loop with T cells. As a therapeutic strategy, it is crucial to disrupt this pro-inflammatory signaling loop [58]. It is possible that abatacept will disrupt this loop. Infliximab is a monoclonal antibody that binds to tumor necrosis factor (TNF)-α to curb pro-inflammatory signaling and may also disrupt the signaling loop [59,60]. ACTIV-1 closed to enrollment on 30 December 2021; results are expected in mid-2022.

Outpatients are being evaluated in a separate NIH study, ACTIV-6. The platform protocol will enroll up to 15,000 participants around the United States in an outpatient setting with a confirmed polymerase-chain reaction (PCR) or antigen test for SARS-CoV-2 and is expected complete enrollment between December 2022 and March 2023 [8,9]. ACTIV-6 aims to provide a definitive answer about the therapeutic potential of fluvoxamine, fluticasone, ivermectin and other drugs for outpatients diagnosed with SARS-CoV-2. Because this is an adaptive trial, the study may change as the standard of care evolves. Results are expected in 2023. The therapeutic approach to COVID-19 will undoubtedly change as we learn more about the pathophysiology of SARS-CoV-2 infection. The fundamental underpinning of this strategy is an appreciation that symptomatic disease is driven by misfiring of the human immune system.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This manuscript has not been funded.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–733.
   • **An excellent introduction to the COVID-19pandemic.**
2. Ward SE, Loutfy MR, Blatt LM, et al. Dynamic changes in clinical features and cytokine/chemokine responses in SARS patients treated with interferon alfacon-1 plus corticosteroids. Antivir Ther. 2005;10(2):263–275.
3. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704. **The most important paper about immunomodulators published thus far.
4. Haider T, Gour V, Pandey V, et al. COVID-19 infection: targeting possibilities for treatment. Crit Rev Ther Drug Carrier Syst. 2021;38(3):75–115.
5. Pessoa-Amorim G, Campbell M, Fletcher L, et al. Making trials part of good clinical care: lessons from the RECOVERY trial. Future Healthc J. 2021;8(2):e243–e50.
6. Fernandes M, Brábek J. COVID-19, corticosteroids and public health: a reappraisal. Public Health. 2021;197:48–55.
7. Buchman TG, Draghia-Akli R, Adam SJ, et al. Accelerating coronavirus disease 2019 therapeutic interventions and vaccines-selecting compounds for clinical evaluation in coronavirus disease 2019 clinical trials. Crit Care Med. 2021;49(11):1963–1973. *An excellent overview of the approach to randomized clinical trials.
8. Grobler JA, Anderson AS, Fernandes P, et al. Accelerated preclinical paths to support rapid development of COVID-19 therapeutics. Cell Host Microbe. 2020;28(5):638–645.
9. Hewitt JA, Lutz C, Florence WC, et al. ACTIVating resources for the COVID-19 pandemic: in Vivo models for vaccines and therapeutics. Cell Host Microbe. 2020;28(5):646–659.

10. Holz M, Mayerl J, Goli S. Early days of the pandemic-The association of economic and socio-political country characteristics with the development of the COVID-19 death toll. PLoS One. 2021;16(8): e0256736.
11. Moghadas SM, Galvani AP. The unrecognized death toll of COVID-19 in the United States. Lancet Reg Health Am. 2021;1:100033.
12. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA. 2021;325(9):855–864.
13. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for Covid-19 - Interim WHO solidarity trial results. N Engl J Med. 2021;384(6):497–511.
14. Bsteh G, Dürauer S, and Assar H, et al. Humoral immune response after COVID-19 in multiple sclerosis: a nation-wide Austrian study. Mult Scler. 2021;11:13524585211049391.
15. Clark NM, Janaka SK, and Hartman W, et al. Anti-SARS-CoV-2 IgG and IgA antibodies in COVID-19 convalescent plasma do not facilitate antibody-dependent enhance of viral infection. bioRxiv. 2021;37:2911–2925.
16. Desimmie BA, Raru YY, and Awadh HM, et al. Insights into SARS-CoV-2 persistence and its relevance. Viruses. 2021;13 (6):1141–1152.
17. Ding C, He J, Zhang X, et al. Crucial mutations of spike protein on SARS-CoV-2 evolved to variant strains escaping neutralization of convalescent plasmas and RBD-Specific monoclonal antibodies. Front Immunol. 2021;12:693775.
18. Khaedir Y, Kartika R. Perspectives on targeting IL-6 as a Potential Therapeutic Strategy for COVID-19. J Interferon Cytokine Res. 2021;41(2):37–43.
19. Doyle EB, Bentley D, and Dodds MG. COVID-19 acute respiratory distress syndrome: a simulation study of the effects of combination therapy with tocilizumab and siltuximab. Br J Clin Pharmacol. 2021;38:3143–3158.
- **An interesting overview of interleukin6 inhibition.**
20. Gritti G, Raimondi F, Bottazzi B, et al. Siltuximab downregulates interleukin-8 and pentraxin 3 to improve ventilatory status and survival in severe COVID-19. Leukemia. 2021;35(9):2710–2714.
21. Meira F, Albiach L, Carbonell C, et al. Experience with the use of siltuximab in patients with SARS-CoV-2 infection. Rev Esp Quimioter. 2021;34(4):337–341.
22. Udwadia Z, Malu KN, R Tripathi AK. The case against tocilizumab. J Assoc Physicians India. 2021;69(4):11–12.
23. Chen YW, Liao HT. Tocilizumab alleviates cytokine storm with acute respiratory distress syndrome in severe SARS-CoV-2 infection in Taiwan. Intern Med J. 2021;51(9):1543–1544. *An important overview of cytokine storm.
24. Amin S, Rahim F, Bahadur S, et al. The effect of tocilizumab on inflammatory markers in survivors and non-survivors of severe COVID-19. J Coll Physicians Surg Pak. 2021;31(1):S7–S10.
25. Tsai A, Diawara O, Nahass RG, et al. Impact of tocilizumab administration on mortality in severe COVID-19. Sci Rep. 2020;10(1):19131.
26. Morales-Avalos A, Vargas-Ponce KG, Idrogo-Alfaro JJ, et al. Experience of using tocilizumab in patients with COVID-19 from a referral hospital in Peru. Rev Peru Med Exp Salud Publica. 2021;38(2):360–362.
27. Emadi A, Chua JV, Talwani R, et al. Safety and efficacy of imatinib for hospitalized adults with COVID-19: a structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21(1):897.
28. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–1645.
29. Brown MJ, Alazawi W, Kanoni S. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19. N Engl J Med. 2021;385(12):1147.
30. Mahroum N, Watad A, and Bridgewood C, et al. Systematic review and meta-analysis of tocilizumab therapy versus standard of care in over 15,000 COVID-19 pneumonia patients during the first eight months of the pandemic. Int J Environ Res Public Health. 2021;18(17):1027–1040.
31. Mouffak S, Shubbar Q, Saleh E, et al. Recent advances in management of COVID-19: a review. Biomed Pharmacother. 2021;143:112107.
32. Cheng Q, Chen J, and Jia Q, et al. Efficacy and safety of current medications for treating severe and non-severe COVID-19 patients: an updated network meta-analysis of randomized placebo-controlled trials. Aging (Albany NY). 2021;13(undefined):899–911.
33. García-García JA, Pérez-Quintana M, and Ramos-Giráldez C, et al. Anakinra versus baricitinib: different strategies for patients hospitalized with COVID-19. J Clin Med. 2021;10(17):706–721.
34. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384 (9):795–807. **An excellent paper on the therapeutic potential of baricitinib in patietnts with COVID19. **An excellent paper on the therapeutic potential of baricitinib in patietnts with COVID19.
35. Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385 (5):406–415.
36. Mornese Pinna S, Lupia T, Scabini S, et al. Monoclonal antibodies for the treatment of COVID-19 patients: an umbrella to overcome the storm? Int Immunopharmacol. 2021;101(Pt A):108200.
37. Claassen V, Davies JE, Hertting G, et al. Fluvoxamine, a specific 5-hydroxytryptamine uptake inhibitor. Br J Pharmacol. 1977;60 (4):505–516.
38. Saletu B, Schjerve M, Grünberger J, et al. Fluvoxamine-a new serotonin re-uptake inhibitor: first clinical and psychometric experiences in depressed patients. J Neural Transm. 1977;41(1):17–36.
39. Sukhatme VP, Reiersen AM, Vayttaden SJ, et al. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. Front Pharmacol. 2021;12:652688.
40. Almási N, Török S, and Valkusz Z, et al. Sigma-1 receptor engages an anti-inflammatory and antioxidant feedback loop mediated by peroxiredoxin in experimental colitis. Antioxidants (Basel). 2020;9 (11):2111–2121.
41. Faraj BA, Olkowski ZL, Jackson RT. Expression of a high-affinity serotonin transporter in human lymphocytes. Int J Immunopharmacol. 1994;16 (7):561–567.
42. Zedan M, Attia G, Zedan MM, et al. Clinical asthma phenotypes and therapeutic responses. ISRN Pediatr. 2013;2013:824781.
43. Valera FC, Umezawa K, Brassesco MS, et al. Suppression of inflammatory cytokine secretion by an NF-κB inhibitor DHMEQ in nasal polyps fibroblasts. Cell Physiol Biochem. 2012;30(1):13–22.
44. Rafiee L, Hajhashemi V, Javanmard SH. Fluvoxamine inhibits some inflammatory genes expression in LPS/stimulated human endothelial cells, U937 macrophages, and carrageenan-induced paw edema in rat. Iran J Basic Med Sci. 2016;19(9):977–984.
45. Williamson PA, Short PM, Vaidyanathan S, et al. Inhaled and systemic corticosteroid response in severe asthma assessed by alveolar nitric oxide: a randomized crossover pilot study of add-on therapy. Br J Clin Pharmacol. 2013;75(1):93–102.
46. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA. 2020;324(22):2292–2300.
47. Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. Open Forum Infect Dis. 2021;8(2):ofab050.
48. Reis G, Dos Santos Moreira-Silva EA, and Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2021;81:4331–4339.
49. Singh CV, Jain S, Parveen S. The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in dysgeusia in COVID-19 patients. Am J Otolaryngol. 2021;42(3):102892.
50. Zilla ML, Keetch C, Mitchell G, et al. SARS-CoV-2 serologic immune response in exogenously immunosuppressed patients. J Appl Lab Med. 2021;6(2):486–490.
51. Singh CV, Jain S, Parveen S, et al. The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in taste dysgeusia in COVID-19 patients. Am J Otolaryngol. 2021;42(4):103009.
52. Caldwell JM, Blanchard C, Collins MH, et al. Glucocorticoid-regulated genes in eosinophilic esophagitis: a role for FKBP51. J Allergy Clin Immunol. 2010;125(4):879–88.e8.

53. Brown M, Phillips CB, Ciszek K, et al. Children in the ACT with asthma–are they taking preventer medication according to guidelines? Aust Fam Physician. 2010;39(3):146–149.
54. Lechien JR, Hoch CC, Vaira LA, et al. The interest of fluticasone nasal spray in COVID-19 related anosmia is still not demonstrated. Am J Otolaryngol. 2021;42(4):103008.
55. Yavuz S, and Komsuoğlu ÇFI. Antiviral treatment of COVID-19: an update. Turk J Med Sci. 2021;19:2004–2015 .
56. Cardwell K, O Murchu E, and Byrne P, et al. Pharmacological interventions to prevent Covid-19 disease: a rapid review. Rev Med Virol. 2021;39:e2299.
57. Angelino G, Cifaldi C, and Zangari P, et al. Gastric cancer, inflammatory bowel disease and polyautoimmunity in a 17-year-old boy: CTLA-4 deficiency successfully treated with abatacept. Eur J Gastroenterol Hepatol. 2021;22:806–821.
58. Grant RA, Morales-Nebreda L, Markov NS, et al. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Nature. 2021;590(7847):635–641.
59. Argüelles-Arias F, Fernández Álvarez P, and Castro Laria L, et al. Switch to infliximab subcutaneous during SARS-CoV-2 pandemic: preliminary results. Rev Esp Enferm Dig. 2021;31:1765–1779.
• **An intriguing look at interleukin6 inhibition in COVID19.**
60. Attiq A, Yao LJ, Afzal S, et al. The triumvirate of NF-κB, inflammation and cytokine storm in COVID-19. Int Immunopharmacol. 2021;101(Pt B):108255.