

REVIEW

The systemic pro-inflammatory response: targeting the dangerous liaison between COVID-19 and cancer

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Available online 8 April 2021

Inflammation is an established driver of severe SARS-CoV-2 infection and a mechanism linked to the increased susceptibility to fatal COVID-19 demonstrated by patients with cancer. As patients with cancer exhibit a higher level of inflammation compared with the general patient population, patients with cancer and COVID-19 may uniquely benefit from strategies targeted at overcoming the unrestrained pro-inflammatory response. Targeted and non-targeted anti-inflammatory therapies may prevent end-organ damage in SARS-CoV-2-infected patients with cancer and decrease mortality. Here, we review the clinical role of selective inhibition of pro-inflammatory interleukins, tyrosine kinase modulation, anti-tumor necrosis factor agents, and other non-targeted approaches including corticosteroids in their roles as disease-modulating agents in patients with COVID-19 and cancer. Investigation of these therapeutics in this highly vulnerable patient group is posited to facilitate the development of tailored therapeutics for this patient population, aiding the transition of systemic inflammation from a prognostic domain to a source of therapeutic targets.

Key words: COVID-19, SARS-CoV-2, cancer, inflammation, immune modulation

INTRODUCTION

The pathophysiology of COVID-19, the pandemic disease resulting from infection by SARS-CoV-2, relies only in part on the direct cytopathic effect of the virus, with the host response proving central in determining end-organ damage.¹⁻³ Accumulating evidence suggests that dysfunctional innate and adaptive immune responses contribute to disease progression, as exemplified by heightened levels of inflammatory markers in serum from severely ill patients.¹ Patients with cancer face worse prognosis from COVID-19 compared with the general patient population, with case fatality rates (CFRs) ranging between 17% and 33% in

patients with cancer, compared with 1%-5% of the general population with COVID-19.⁴⁻⁸

The presence of a pre-existing pro-inflammatory diathesis at time of SARS-CoV-2 infection may explain the predisposition of patients with cancer to severe COVID-19 and increased risk of death: mortality from COVID-19 has been, in fact, linked to pro-inflammatory cytokine excess leading to an unopposed immune response with detrimental multisystem effects.^{1,2,9-13} Oncologic disease and its associated treatments predispose patients with cancer to an intrinsic inflammatory state through neutrophilia resulting from tumor-produced immune-modulating elements such as granulocyte colony-stimulating factor (G-CSF); elevation of circulating C-reactive protein in carcinomas; increased serum ferritin produced by tumor-associated macrophages; and potentially inflammatory G-CSF therapy for treatment-related immunodeficiency.¹⁴⁻¹⁷ In a recent study, we demonstrated that a number of pro-inflammatory biomarkers including the neutrophil-lymphocyte ratio (NLR), prognostic nutritional index, modified Glasgow prognostic score, and prognostic index measured at time of SARS-CoV-2 infection identify patients with cancer at greater risk of mortality from COVID-19.¹⁸ In particular, hypoalbuminemia, the reduction of expression of albumin that is part of a negative phase reaction largely driven by interleukin 6

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(IL-6), and lymphocytopenia, a diagnostic hallmark of SARS-CoV-2 infection secondary to viral replication and systemic cytokine excess, are optimal features to define patients with adverse outcomes from COVID-19 when considered together as the OnCovid Inflammation Score (OIS).¹⁸⁻²² The OIS is derived from albumin and lymphocyte counts, with a lower score indicating hypoalbuminemia and lymphocytopenia and a greater score indicating higher albumin and lymphocyte counts.^{18,23} Patients in the validation set with an OIS ≤ 40 displayed an overall survival (OS) of 40 days (95% confidence interval 8-72 days) and a CFR of 47.6%, while patients with a low-risk OIS >40 did not reach median OS ($P < 0.0001$) and presented a CFR of 18.8% ($P < 0.0001$).¹⁸

While prioritization of vaccination against SARS-CoV-2 is expected to reduce the toll of SARS-CoV-2 on patients with cancer, the development of anti-COVID-19 therapeutics continues in parallel at a rapid pace to ensure patients diagnosed with the disease can be protected from its deleterious consequences.²⁴ Innate and adaptive immune dysfunction is a shared mechanism that characterizes the host response against cancer as well as COVID-19.^{25,26} In particular, systemic release of a number of pro-inflammatory mediators including IL-6, interferon- γ , and tumor necrosis factor- α (TNF- α) is common in patients with advanced malignancies and underlies several of the systemic consequences of cancer such as anorexia, cachexia, nutritional decline, and sarcopenia or, in hematologic malignancies, 'B symptoms' that are pathognomonic and prognostic in patients with lymphoma.²⁷⁻²⁹ In COVID-19, acute and unopposed release of pro-inflammatory mediators is responsible for a much more clinically serious cytokine release syndrome (CRS), which has been linked with respiratory compromise, end-organ damage, and mortality from SARS-CoV-2.^{1,30-35}

Besides its role as a prognostic domain in identifying patients with adverse clinical course, up-regulation of pro-inflammatory pathways lends itself as a potential source of putative therapeutic targets in COVID-19.¹ Treatments targeting COVID-19-induced inflammation may provide a therapeutic advantage in patients with concomitant cancer and COVID-19 over the general patient population through modulation of cancer- and COVID-19-related synergistic inflammation.⁹ In this review, we evaluate evidence and rationales for the use of both targeted and non-targeted therapeutic agents aimed at attenuating the inflammatory response in patients with both cancer and COVID-19. To achieve this aim, we focused on selected therapeutic agents with recognized or postulated efficacy on the basis of their mechanisms of action as shown in Figure 1.

TARGETED THERAPIES

IL-6

Both advanced cancer and severe COVID-19 are characterized by systemic excess of IL-6, a pro-inflammatory cytokine produced predominantly by tissue-resident macrophages

upon recognition of damage- and pathogen-associated molecular patterns (DAMPs and PAMPs) and capable of stimulating acute phase protein synthesis, regulating neutrophil recruitment, and inducing repression of regulatory T cells.^{1,10,36-38} In patients with cancer, increased IL-6 levels are linked to poorer prognosis via increased angiogenesis in solid tumors through up-regulation of vascular endothelial growth factor; tumor proliferation through enhanced transcription of signal transducer and activator of transcription 3 (STAT3), an oncogenic transcription factor; and immune dysfunction through modulation of T cell activity.³⁹⁻⁴² Heightened concentration of IL-6 has also been linked to increased mortality in patients with severe COVID-19 and consequently proposed as a therapeutic target.^{1,43-45} IL-6 receptor antagonists may offer a therapeutic advantage in patients with cancer and COVID-19 over the unselected patient population through prevention of IL-6-mediated synergistic inflammation, especially considering the use of IL-6 receptor antagonists against another pathophysiologic similarity between COVID-19 and cancer: CRS.^{9,46-49} CRS is an acute inflammatory crisis resulting from an increase in circulating cytokines not only associated with severe COVID-19, but also with bispecific monoclonal antibodies and adoptive cell therapies including chimeric antigen receptor T-cell therapies.^{46,47,49,50} Accordingly, treatment with tocilizumab, an anti-IL-6 receptor inhibitor traditionally utilized for rheumatoid arthritis, has been proposed as a therapy for severe COVID-19 in view of its utility in treating CRS.⁵¹⁻⁵⁵ Initially, retrospective and prospective analyses of the administration of tocilizumab to patients with COVID-19-associated pneumonia admitted to hospital revealed that receipt of tocilizumab significantly reduces mortality.^{51,53} Disappointingly, the phase III COVACTA trial of tocilizumab in hospitalized patients with COVID-19-associated pneumonia showed no reduction in 28-day mortality despite evidence of improvement in duration of hospital admission.^{54,56} Inclusion criteria may explain differing outcomes, such as the heterogeneity in the presentation of severe COVID-19.⁵⁴ In the more recent phase III EMPACTA trial of tocilizumab plus standard of care anti-COVID-19 therapy versus placebo in patients hospitalized with severe COVID-19-associated pneumonia, treatment with tocilizumab led to a 44% reduction in the risk of progression to mechanical ventilation or death by day 28; although, overall mortality by day 28 did not significantly differ between patients receiving tocilizumab or placebo (10.4% versus 8.6%, $P = 0.5146$).⁵² Clinical benefit from tocilizumab was restricted to patients not requiring mechanical ventilation, suggesting IL-6 blockade to be an effective treatment only at certain stages of COVID-19 severity.⁵²

Sarilumab, an IL-6 receptor antagonist utilized for rheumatoid arthritis, demonstrates similarly mixed efficacy against COVID-19 and failure to meet primary endpoints.^{57,58} In an open-label study of sarilumab against severe COVID-19, patients receiving sarilumab demonstrated no differences in clinical improvement (61% sarilumab versus 64% standard of care, $P = 0.94$) or mortality (7%

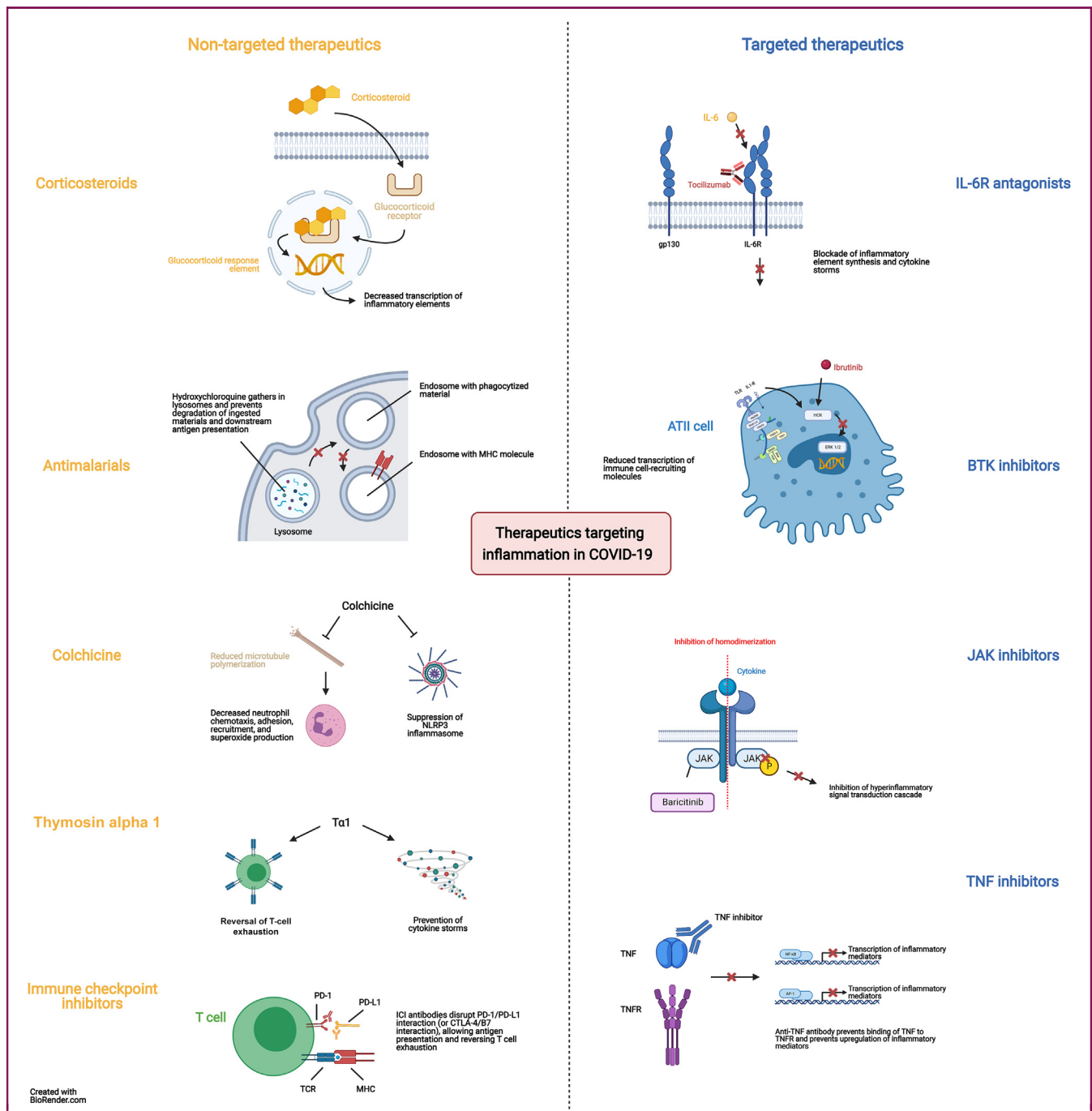


Figure 1. Therapeutics targeting inflammation in COVID-19.

AP-1, activator protein 1; ATII, alveolar epithelial type II; BTK, Bruton’s tyrosine kinase; CTLA4, cytotoxic T-lymphocyte-associated protein 4; ERK 1/2, extracellular signal-regulated protein kinase 1/2; HCK, hematopoietic cell kinase; ICI, immune checkpoint inhibitor; IL-1-R, interleukin 1 receptor; IL-6, interleukin 6; IL-6R, interleukin 6 receptor; JAK, Janus kinase; MHC, major histocompatibility complex; NF- κ B, nuclear factor kappa B; NLRP3, neutrophil-lymphocyte ratio family pyrin domain containing 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T cell receptor; TLR, toll-like receptor; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor.

sarilumab versus 18% standard of care, $P =$ not significant) compared with patients receiving standard of care.⁵⁷ Sarilumab treatment only demonstrated clinical improvement and faster recovery from COVID-19 in the subset of patients with minor lung consolidation, reinforcing opportune timing of IL-6 blockade as a critical factor for the efficacy of IL-6 receptor antagonists against COVID-19.⁵⁷ This claim is supported by results from a single-center study in Italy: lower circulating IL-6 at baseline and lower NLR, features of earlier

disease, were associated with a more favorable response to sarilumab therapy for COVID-19 and clinical improvement.⁵⁸ The CORIMUNO-VIRO study of sarilumab for COVID-19 was discontinued due to futility ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04341870) identifier: NCT04341870); however, this lack of observed clinical benefit may have resulted from administration of sarilumab at an inopportune time in the disease course.

Evolving clinical experience suggests the need for more precise stratification of severity in hospitalized COVID-19

patients in order to maximize benefit from IL-6 blockade. The predictive role of baseline pro-inflammatory status warrants further investigation, given the efficacy of sarilumab only in patients with lower circulating baseline IL-6.⁵⁸ Identification of predictive biomarkers of response to these expensive therapies may aid a more judicious clinical use, especially given the heterogeneity emerging from clinical trials and the lack of influence over mortality seen in unselected hospitalized patients with COVID-19.^{10,52,54,56-58} Importantly, IL-6 blockade may fail to ameliorate severe disease due to interference with the compensatory anti-inflammatory response, a reaction to inflammation that involves increased production of anti-inflammatory cytokines, primarily IL-10, and consequent restoration of homeostasis.⁵⁹ IL-6 blockade may complicate the mounting of the compensatory anti-inflammatory response and subsequent resolution of the inflammatory state.⁵⁹ Duration and timing of the anti-inflammatory response are linked to outcomes in patients with infectious diseases.⁵⁹

Importantly, interleukin signaling is redundant and pleiotropic; therefore, inhibition of a single pathway may not result in clinical benefit.⁶⁰ While studies have included patients with concomitant cancer and COVID-19 being treated with tocilizumab in their cohorts, the outcomes of these patients have not been independently analyzed.⁸ Whether cancer patients may represent a population exquisitely sensitive to IL-6 inhibition remains to be ascertained.

Bruton's tyrosine kinase

A relatively unexplored avenue of therapy for COVID-19 may be a drug class commonly utilized in the treatment of certain hematologic malignancies: Bruton's tyrosine kinase (BTK) inhibitors. Up-regulation and constitutive activation of BTK results in B-cell proliferation and survival and is a pathophysiologic mechanism of B-cell malignancies including lymphomas and leukemias.^{61,62} BTK inhibitors are currently utilized in treatment regimens for some B-cell malignancies including mantle cell lymphoma and chronic lymphocytic leukemia (CLL).^{63,64} The BTK inhibitor ibrutinib has been proposed as a novel therapeutic for COVID-19, and the second generation BTK inhibitor acalabrutinib has exhibited efficacy against COVID-19 in a small cohort of severely ill patients receiving oxygen when administered as a salvage therapy.^{65,66} Traditionally utilized as a BTK inhibitor in CLL, ibrutinib also serves as an inhibitor of hematopoietic cell kinase (HCK), a kinase involved in immune cell recruitment within the lung by alveolar type II cells.⁶⁵ Attenuation of immune cell recruitment by these alveolar cells via ibrutinib-mediated HCK inhibition may reduce pulmonary inflammation in patients with severe COVID-19.^{65,67} In a cohort of six patients with concomitant Waldenström macroglobulinemia (WM), a non-Hodgkin B-cell lymphoma, and COVID-19 already receiving ibrutinib for WM at the time of COVID-19 diagnosis, patients receiving the recommended 420 mg/day dosage of ibrutinib for WM did not require hospitalization or develop COVID-19-

induced dyspnea, while the patient receiving the 140 mg/day dosage of ibrutinib demonstrated rapid clinical deterioration and required mechanical ventilation, but quickly recovered following increase of ibrutinib to 420 mg/day.^{65,68} Exploration of the efficacy of ibrutinib in the treatment of COVID-19 will elucidate the therapeutic effects of acalabrutinib administration observed in severely ill patients with COVID-19.⁶⁶ Acalabrutinib does not exhibit binding with HCK and is highly specific for BTK; therefore, acalabrutinib may improve clinical status in a non-HCK-dependent manner.⁶⁹ Exploration of these avenues will also provide further insight into the interplay between the virus-mediated cytopathic and immune system-mediated inflammatory effects of COVID-19 given the status of alveolar cells as both entry points for SARS-CoV-2, due to their surface expression of angiotensin-converting enzyme 2 (ACE2), the receptor exploited by SARS-CoV-2, and mediators of pulmonary inflammation.⁶⁵

Study of ibrutinib or acalabrutinib treatment in patients with cancer and COVID-19, with an emphasis on patients with thoracic malignancies possessing heightened baseline pulmonary inflammation before SARS-CoV-2 infection, is necessary to understand if clinical improvement through attenuation of local pulmonary inflammation via ibrutinib or if clinical improvement through a separate mechanism via acalabrutinib improves outcomes from COVID-19 and is a viable targeted COVID-19 therapy by primary tumor type.^{65,66,70} Currently, the Academic and Community Cancer Research United is preparing to recruit >130 patients with concomitant B-cell malignancy and COVID-19 to a prospective study exploring ibrutinib treatment of COVID-19 in this population ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04665115) identifier: NCT04665115).

Janus kinase

Janus kinase (JAK) inhibitors are a well-established therapeutic class utilized in a range of autoimmune and inflammatory diseases.⁷¹ JAK activation is critical for transcription of cytokines via downstream activation of STATs; necessary for cell differentiation and hematopoiesis; and has been linked in its constitutively activated forms to leukemia development via cancer cell proliferation.⁷² JAK inhibitors attenuate inflammation in rheumatoid arthritis through reduction of cytokine and inflammatory element transcription and are being explored as therapeutics for leukemias due to inhibition of leukemic cell proliferation and reduction of the neoplasm-induced inflammatory state.^{73,74} JAK inhibitors accordingly may serve as an anti-COVID-19 therapeutic through reduction of circulating cytokines and additionally confer preferential benefit for patients with concomitant COVID-19 and hematologic malignancies associated with aberrant JAK signaling.^{72,74} The JAK inhibitor ruxolitinib, which exhibits antileukemic activity, has been studied for its immunosuppressive effects in severe COVID-19.⁷⁵⁻⁷⁷ Administration of ruxolitinib did not improve outcomes from COVID-19 in severely ill patients but was associated with faster clinical improvement and improved chest

computed tomography.⁷⁵ The JAK inhibitor baricitinib, a therapeutic utilized for anti-inflammatory effects in rheumatoid arthritis, has been studied in combination with the antiviral remdesivir in patients hospitalized with COVID-19.^{78,79} Patients receiving baricitinib plus remdesivir demonstrated improved clinical status and faster recovery times compared with patients receiving remdesivir alone.⁷⁸ Despite the modest therapeutic efficacy exhibited by remdesivir and baricitinib in patients with severe COVID-19, JAK inhibitors may improve outcomes from CRS in COVID-19 through inhibition of initial viral infection and endocytosis via off-target effects of baricitinib and reduction of expression of transcription of inflammatory cytokines.^{72,80} As CRS is a shared feature of cancer and severe COVID-19, patients with cancer may preferentially benefit from JAK inhibitor therapy for severe COVID-19.^{48,49} The University of Southern California (USC) is recruiting patients to a study investigating baricitinib alone and in combination with other therapeutics as a treatment of moderate and severe COVID-19 in patients with cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04373044) identifier: NCT04373044). Another phase III clinical study is recruiting hospitalized patients with severe COVID-19 with or without cancer to receive pacritinib, an oral JAK2 and fms-like tyrosine kinase 3 (FLT3) inhibitor, as a treatment of COVID-19 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04404361) Identifier: NCT04404361).⁸¹

Tumor necrosis factor

Tumor necrosis factor (TNF), a pro-inflammatory cytokine family up-regulated in autoimmune disorders, infectious diseases, and cancer, regulates the expression of reactive oxygen species and other pro-inflammatory cytokines through the nuclear factor kappa-light-chain-enhancer of activated B cells and activator protein 1 pathways.⁸² TNF family cytokines are primarily secreted by macrophages, but also produced in smaller quantities by lymphocytes.⁸² Higher baseline circulating TNF cytokines have been linked to cachexia, sepsis, and poorer prognoses from oncologic disease.⁸² In patients with cancer, TNF exhibits situation-dependent antitumoral or protumoral effects.⁸³ TNF has demonstrated inhibition of angiogenesis and tumor growth in solid tumor models.⁸³ Conversely, TNF has been identified as a causative agent in skin, hepatic, and gastrointestinal carcinogenesis.⁸³ Patients with severe COVID-19 exhibit higher circulating TNF, and higher baseline TNF is associated with poorer outcomes from COVID-19.^{1,84} Accordingly, anti-TNF therapy has been proposed to counter COVID-19 hyperinflammation.⁸⁴ Anti-TNF therapeutics have been hypothesized to have broader anti-inflammatory effects than IL-6 receptor antagonists, as TNF blockade broadly reduces the expression of pro-inflammatory mediators and clotting biomarkers, effects not observed from IL-6 blockade.⁸⁵ TNF also facilitates SARS-CoV entry through ACE2 and may extend similar assistance to SARS-CoV-2.^{86,87} Large, randomized trials are lacking: case and small cohort reports comprise the current body of evidence for anti-TNF as a COVID-19 therapeutic.⁸⁷⁻⁸⁹

A case report revealed that a patient receiving the TNF- α inhibitor etanercept and the antimetabolite methotrexate for spondyloarthritis, who later developed COVID-19, did not require intensive care, and did not develop respiratory distress or lymphopenia.⁸⁸ A survey distributed in Lombardy, Italy, to 320 patients receiving immune-modulating therapeutics for chronic arthritis, with 52% of patients receiving TNF inhibitors, identified four patients with confirmed COVID-19, four patients with symptoms highly suggestive of COVID-19, and five patients with contact with a known COVID-19 case.⁸⁹ From this group, only one patient required hospital admission for COVID-19 and subsequently recovered; importantly, this study can only serve as anecdotal evidence of the association between immune-modulating therapeutics and COVID-19 risk.⁸⁹ In Pavia, Italy, three patients receiving anti-TNF therapy for rheumatological diseases who contracted COVID-19 did not develop dyspnea or require hospitalization.⁸⁷ No data exists for patients with cancer and COVID-19 receiving anti-TNF therapy as a COVID-19 therapeutic. Patients with rheumatological diseases have comprised the current focus of anti-TNF therapy and implications for COVID-19 disease course due to concerns regarding this immunosuppressive treatment and COVID-19 risk.⁸⁷ Patients with cancer and COVID-19 warrant study, as TNF imbalance supports tumor initiation, invasion, and metastasis and is a noted serological marker of severe COVID-19.⁹⁰ Anti-TNF treatment may extend preferential benefit to patients with cancer and COVID-19 who possess heightened baseline TNF, but anti-TNF therapy may also complicate oncologic disease management, as TNF exhibits both protumoral and antitumoral effects.⁸³ While short-term anti-TNF treatment has not been associated with cancer progression, the effects of anti-TNF therapies in patients with cancer and infectious disease remain to be tested.⁸⁴ A search on [ClinicalTrials.gov](https://clinicaltrials.gov) revealed no clinical trials currently investigating anti-TNF treatment specifically for patients with cancer and COVID-19.

NON-TARGETED THERAPIES

Corticosteroids

Corticosteroids are glucocorticoid hormones utilized for their broad anti-inflammatory and lymphocytolytic effects in a variety of diseases including asthma, leukemias, and rheumatoid arthritis.⁹¹⁻⁹³ Corticosteroids penetrate the cellular membrane; bind to glucocorticoid receptors thus allowing glucocorticoid receptor homodimerization; enter the nucleus; and repress transcription of inflammatory mediators via interaction with glucocorticoid response elements and interference with transcription.^{92,94} In patients with leukemia, steroids alter oncogene expression and induce cell cycle arrest and apoptosis.⁹² Current treatment protocols for COVID-19 include corticosteroids such as dexamethasone, but knowledge gaps persist regarding the timing and duration of steroid therapies for COVID-19.⁹⁵ The RECOVERY trial demonstrated that dexamethasone administration resulted in reduced mortality among patients with COVID-19 receiving oxygen therapy, including

those receiving invasive mechanical ventilation and non-invasive methods of oxygenation.⁹⁶ Patients who did not require respiratory support exhibited no benefit from dexamethasone receipt.⁹⁶ Dexamethasone has also been associated with decreased mortality in patients with severe COVID-19 in a prospective meta-analysis by the World Health Organization (WHO).^{96,97} Taken together, these results provide support for dexamethasone as a treatment of severe COVID-19, but not for mild cases.

Patients with cancer and severe COVID-19 may benefit from corticosteroid therapy through prevention of synergistic inflammation. Interestingly, the COVID-19 and Cancer Consortium (CCC19) has shown that administration of high-dose corticosteroids is not associated with mortality benefit in patients with COVID-19 and cancer, but administration of high-dose corticosteroids in combination with any other anti-COVID-19 therapeutic is associated with increased mortality.⁹⁸ It is important to note that the exact role of corticosteroids in patients with cancer and COVID-19 is difficult to establish, as corticosteroids are often administered for symptom palliation; therefore, this therapeutic may demonstrate increased mortality only when utilized in combination with another COVID-19 therapeutic as observed by the CCC19, due to worse baseline clinical conditions of patients rather than a disease-worsening effect of corticosteroid treatment.^{98,99} Further, steroid-induced immune suppression may be compounded by the concomitant receipt of anticancer treatments that suppress the immune system including chemotherapy.^{100,101} Additionally, patients included in the CCC19 study were not necessarily severely ill from COVID-19, while patients in the RECOVERY trial and WHO meta-analysis were severely ill, making the role of corticosteroids harder to elucidate.⁹⁶⁻⁹⁸ Benefit of corticosteroid therapy may be limited to severely ill patients or patients receiving oxygen therapy. For patients with cancer and severe COVID-19 requiring oxygen therapy, corticosteroid therapy may prevent synergistic inflammation and provide an opportunity to identify inflammatory biomarkers predictive of steroid benefit. Corticosteroid therapy may also preferentially benefit patients with leukemia and COVID-19, especially patients with childhood acute lymphoblastic leukemia, as steroids may exhibit dual anti-COVID-19 and anti-neoplastic action.⁹² Importantly, treatment providers must consider potentially compounded immune suppression resulting from concomitant receipt of steroidal and anticancer therapeutics in patients with cancer and COVID-19.¹⁰⁰⁻¹⁰² Further study will reveal differences in immune system response between patients with cancer and the general patient population.

Antimalarials

Hydroxychloroquine and chloroquine, widely used antimalarial agents, were explored as therapeutics for COVID-19 due to their potential for blockage of viral entry via interference with pH-dependent endosomes and attenuation of systemic cytokine release by interference of the antimalarial agents with antigen processing and autoantigen

presentation.^{103,104} The RECOVERY trial revealed a lack of support for hydroxychloroquine as an anti-COVID-19 therapeutic.¹⁰⁵ Hydroxychloroquine administration demonstrated the following non-significant associations: increased mortality; reduced likelihood of being discharged alive from the hospital within 28 days; increased incidence of mechanical ventilation; and increased occurrence of cardiac deaths but not cardiac arrhythmias.¹⁰⁵ Hydroxychloroquine administration also raised concerns regarding potential for cardiotoxicity; accordingly, the RECOVERY trial excluded patients with prolonged QTc intervals from the hydroxychloroquine arm.¹⁰⁵ In contrast, OnCovid demonstrated reduced mortality rates among patients with concomitant cancer and COVID-19 exposed to antimalarials compared with patients receiving no anti-COVID-19 therapy; although, estimation of a precise effect of antimalarials over other co-administered therapies cannot be fully appreciated due to the retrospective design.⁴ These results differ from those of the CCC19 study.^{4,98} In the CCC19 cohort, patients with cancer and COVID-19 receiving hydroxychloroquine were characterized by higher mortality compared with untreated controls and patients receiving any other anti-COVID-19 therapeutics.⁹⁸ A clinical trial hosted by Memorial Sloan Kettering Cancer Center is recruiting patients with cancer receiving radiotherapy to study the potential of hydroxychloroquine to prevent SARS-CoV-2 infection ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04381988) identifier: NCT04381988). USC is recruiting patients to study baricitinib alone or in combination with anti-COVID-19 therapeutics, including hydroxychloroquine, to treat moderate and severe COVID-19 in patients with cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04373044) identifier: NCT04373044). Further studies will clarify the role of hydroxychloroquine as an anti-COVID-19 therapeutic, but serious safety concerns, including potential cardiotoxicity, may be heightened in patients with cancer who are predisposed to prolonged QTc due to anticancer therapeutics.¹⁰⁵⁻¹⁰⁸ The practice of routinely prescribing antimalarials for COVID-19 has largely fallen out of favor following publication of the results of RECOVERY, which showed no benefit from the utilization of these therapies in the context of SARS-CoV-2 infection.¹⁰⁵

Colchicine

Colchicine, an anti-gout agent with broad anti-inflammatory effects, has been proposed as a putative therapeutic agent for COVID-19.¹⁰⁹⁻¹¹¹ Colchicine disrupts microtubule polymerization and gathers preferentially in leukocytes.¹¹² Inflammation is broadly inhibited by colchicine: this alkaloid therapeutic inhibits neutrophil chemotaxis, adhesion, recruitment, and superoxide production, and suppresses the NLR family pyrin domain containing 3 (NLRP3) inflammasome, a component of innate immunity that regulates secretion and activation of stimulators of pyroptosis and pro-inflammatory cytokines.^{112,113} In a single-center cohort study, colchicine treatment exhibited association with better survival compared with standard of care in patients hospitalized with COVID-19-associated pneumonia.¹¹⁴ Furthermore,

treatment with colchicine was independently associated with reduced mortality.¹¹⁴ In a randomized, double-blinded, placebo-controlled trial for moderate and severe COVID-19, colchicine treatment reduced length of oxygen therapy (when required) and length of hospitalization; however, insufficient participants were available to study the effects of colchicine on mortality and COVID-19 severity.¹¹⁵ The GRECCO-19 randomized trial of colchicine in patients hospitalized with COVID-19 revealed reduced clinical deterioration in the group receiving colchicine compared with standard of care and increased time to clinical deterioration in the colchicine arm.¹¹⁶ Patients with cancer and COVID-19 may preferentially benefit from colchicine treatment compared with the general population, as colchicine attenuates shared inflammatory mechanisms between cancer and COVID-19 including formation of neutrophil extracellular traps (NETs) and NLRP3 inflammasome activation.^{112,117-121} Colchicine may prevent NET- and NLRP3-mediated synergistic inflammation in this patient population. A search on [ClinicalTrials.gov](https://www.clinicaltrials.gov) revealed no clinical trials currently investigating colchicine treatment specifically for patients with cancer and COVID-19.

Thymosin alpha 1

Thymosin alpha 1 ($T\alpha 1$), a peptide produced by and isolated from thymic tissue, may ameliorate immune derangement induced by SARS-CoV-2 infection.¹²²⁻¹²⁴ $T\alpha 1$, the active cleavage product of prothymosin alpha, acts broadly in normal physiology to stimulate T-cell maturation, antigen presentation, natural killer (NK) cell activity, and infected dendritic cell activity.¹²⁵ $T\alpha 1$ exerts this broad immune system modulation via interaction with intracellular Toll-like receptors, a protein class responsible for identifying PAMPs in innate immunity, in myeloid and plasmacytoid dendritic cells.^{126,127} Administration of synthetic $T\alpha 1$ has exhibited restoration of immune system homeostasis through lymphoid cell activation in *ex vivo* human immunodeficiency virus-1 samples and through NK cell activation in mouse models of leukemia.^{125,128} In patients with severe COVID-19, $T\alpha 1$ treatment demonstrated association with reduced mortality, improved T-cell counts, and reversal of T-cell exhaustion.¹²⁴ *Ex vivo* $T\alpha 1$ treatment of blood cells from patients with COVID-19 confirmed $T\alpha 1$ prevents cytokine storms and reduces T-cell exhaustion in COVID-19.¹²³ The condition of cytokine excess that accompanies cancer progression and leads to exhausted, or hyporesponsive, T cells is a well-known determinant of prognosis in patients with advanced malignancies.^{35,129,130} It can therefore be hypothesized that patients with cancer and COVID-19 may preferentially benefit from $T\alpha 1$ treatment over the general patient population through reduction of synergistic T-cell exhaustion from both cancer and COVID-19. The phase II PROTHYMOS study is currently investigating $T\alpha 1$ as prophylaxis for patients with cancer and severe COVID-

19.¹³¹ Conclusion of this study and comparative investigation between patients with COVID-19, with or without history of cancer, will help clarify whether a role exists for this therapy in patients with COVID-19 and cancer.

Immune checkpoint inhibitors

A number of cancers are characterized by a lack of anti-tumor T-cell reactivity.¹³² Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1) are immune checkpoint receptors on T cells that prevent uncontrolled immune responses in normal physiology through binding with their respective ligands B7 and programmed death-ligand 1 (PD-L1), inhibiting antigen presentation and consequent T-cell response.¹³² In oncologic disease, these regulators prevent antitumor activity and cancer cell elimination by T cells as some cancer cells express surface B7 and PD-L1.¹³² First utilized for metastatic melanoma, immune checkpoint inhibitors (ICIs) aim to restore anticancer T-cell reactivity through antibody inhibition of CTLA-4/B7 binding and PD-1/PD-L1 binding.¹³³ As severe COVID-19 may cause T-cell exhaustion, ICIs have been postulated to restore T-cell function in critically ill patients; however, only observational registries of patients with COVID-19 and cancer undergoing ICI treatment of oncologic disease exist, and no studies for the general patient population with COVID-19 exist.^{134,135} Although ICIs may exhibit anti-COVID-19 action through reversal of T-cell exhaustion, complications of ICI treatment, including ICI-pneumonitis, raise concern over safety of ICI treatment and necessitate studies balancing the reversal of T-cell exhaustion with the risk of pneumonitis.^{134,136} The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry demonstrated that patients with cancer receiving ICI therapy either alone or in combination with chemotherapy for oncologic disease at the time of COVID-19 diagnosis did not exhibit higher mortality rates.¹³⁵ A multicenter observational study of patients from hospitals in North America, Europe, and Australia revealed that patients with COVID-19 already receiving ICIs for cancer did not present higher mortality than patients with cancer and COVID-19 not receiving ICIs at time of COVID-19 diagnosis.¹³⁷ In a study of patients undergoing PD-1 blockade for lung cancer and later diagnosed with COVID-19, PD-1 blockade receipt did not affect mortality and did not alter circulating IL-6.¹³⁸ While PD-1 blockade may reduce viral load through restoration of effector function, this therapeutic may not reduce systemic inflammation.¹³⁸ While ongoing ICI therapy for cancer does not appear to increase susceptibility to fatal COVID-19, there are no studies of ICIs administered as anti-COVID-19 therapeutics. Study of ICI treatment of SARS-CoV-2 infection in patients with cancer and COVID-19 not previously receiving this antineoplastic therapy will clarify the safety and utility of ICIs for reversal of T-cell exhaustion in infectious disease. Prospective trials of ICIs for COVID-19 for the general patient population will elucidate differences in immune responses and mechanisms

of T-cell exhaustion between patients with or without concomitant oncologic disease. No clinical trials testing ICIs as anti-COVID-19 therapeutics for patients with concomitant cancer and SARS-CoV-2 infection are registered, but nivolumab, a PD-1 inhibitor, is being explored as a therapeutic for obese individuals with COVID-19 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04413838) identifier: NCT04413838). Detailed immune profiling by Hamad Medical Corporation of patients with cancer and COVID-19, including profiling of circulating ICI levels and subsequent COVID-19 outcomes, will clarify patient responses at the molecular level ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04473131) identifier: NCT04473131).

CONCLUSIONS

Accumulating evidence suggests that patients with cancer and COVID-19 may uniquely benefit from therapeutics that attenuate systemic inflammation and consequently prevent synergistic inflammation. The heightened susceptibility of patients with cancer to fatal SARS-CoV-2 infection may result from higher baseline inflammation due to oncological disease subsequently aggravated by infectious disease; however, further study is required to determine the contributions of cancer histology, state, and treatment to inflammation and outcomes from COVID-19. In this review, we described how therapeutic targeting of pathways implicated in the systemic inflammatory response may preferentially benefit patients with cancer over the general patient population. Despite displaying higher CFRs, patients with cancer have not been the focus of specific studies of anti-SARS-CoV-2 therapeutics, perhaps due to the concerns over the confounding effect of malignancy in determining mortality.

The majority of evidence guiding treatment of patients with COVID-19 and cancer has emerged from retrospective registries: none of these studies can substitute prospective, randomized, controlled studies in homogeneous patient populations. Certain areas are still characterized by a significant knowledge gap, and the comparison between prospective versus retrospective evidence emerges perhaps more strongly in the case of corticosteroid therapy, a treatment for which there is a lack of benefit for patients with COVID-19 and cancer, but improved outcomes for the general patient population with COVID-19.⁹⁶⁻⁹⁸

Such level of uncertainty calls for the need to elucidate the utility of anti-inflammatory agents in treating severe COVID-19 in patients with cancer in prospective clinical trials.¹³⁹ The lack of molecular or immunologic stratification is also a major limitation to most studies of COVID-19 therapeutics. Efficient determination of inflammatory marker levels via enzyme-linked immunosorbent assay profiling of patients with severe COVID-19 has been proposed for personalized COVID-19 therapeutic regimens.¹⁴⁰ Especially for patients with a heightened risk for synergistic inflammation, this would aid in rapid determination of the targeted or non-targeted therapy to be utilized. To this end, the COVID-19 antiviral response in a pan-tumor immune monitoring study (CAPTURE), a prospective study

recruiting patients with concomitant cancer and COVID-19, aims to profile the immune responses of these patients to SARS-CoV-2 infection.¹⁴¹ Translational studies similar to CAPTURE will help establish the molecular features underlying the progression of COVID-19 in patients with cancer and facilitate the development of targeted and non-targeted anti-inflammatory agents in patients who are most likely to derive clinical benefit.

The challenge of the global COVID-19 pandemic has proven the utility of cross-field collaboration for drug repurposing and treatment development.^{136,142} Immunoncologists, experienced with immune-modulating therapeutics, have both identified anticancer drugs that may offer therapeutic benefit for COVID-19 and noted similarities between anticancer treatment and COVID-19, including those of ICI-induced pneumonitis and the ground-glass opacities of COVID-19 pneumonia.¹³⁶ As COVID-19 vaccine distribution criteria vary across regions, improved treatments for patients with concomitant cancer and COVID-19 will continue to be an unmet need that may be addressed through immunomodulatory drugs.^{136,143-145}

FUNDING

This work was supported by grant funding from the Wellcome Trust Strategic Fund [grant number PS3416] (to DJP) and acknowledges infrastructural support by the Cancer Research UK Imperial Centre and the Imperial National Institute for Health Research Biomedical Research Centre.

DISCLOSURE

DJP has received lecture fees from ViiV Healthcare and Bayer Healthcare; travel expenses from Bristol-Myers Squibb (BMS) and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, and AstraZeneca; and received research funding (to institution) from Merck Sharp & Dohme (MSD) and BMS. AC has received lecture fees from AstraZeneca, MSD, Novartis, and Astellas and consulting fees/advisory board grants from AstraZeneca, MSD, Roche, and BMS. AG has declared consulting/advisory roles for Roche, MSD, Eli Lilly, Pierre Fabre, Eisai, and Daichii Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, AstraZeneca, Celgene, and Daichii Sankyo; research funds from Eisai, Eli Lilly, and Roche. GP has received advisory board fees from Amgen, AstraZeneca, BMS, Lilly, Merck, MSD, Roche and research funding (to institution) from Amgen, Abbvie, Boehringer, AstraZeneca, BMS, Lilly, Merck, MSD, Roche, Debiopharm, Ipsen, Pfizer, Servier. ER received research funding from Amgen, AstraZeneca, and BMS; travel expenses from AstraZeneca, BMS, Merck, and Roche. All other authors have declared no conflicts of interest.

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