Repurposing of Anticancer Drugs Expands Possibilities for Antiviral and Anti-Inflammatory Discovery in COVID-19

Mihaela Aldea1, Jean-Marie Michot2, Francois-Xavier Danlos3,4, Antoni Ribas5, and Jean-Charles Soria2,4

ABSTRACT

In 2020, the COVID-19 pandemic led to an unprecedented destabilization of the world’s health and economic systems. The rapid spread and life-threatening consequences of COVID-19 have imposed testing of repurposed drugs, by investigating interventions already used in other indications, including anticancer drugs. The contours of anticancer drug repurposing have been shaped by similarities between the pathogenesis of COVID-19 and malignancies, including abnormal inflammatory and immunologic responses. In this review, we discuss the salient positive and negative points of repurposing anticancer drugs to advance treatments for COVID-19.

Significance: Targeting anti-inflammatory pathways with JAK/STAT inhibitors or anticytokine therapies aiming to curb COVID-19–related cytokine storm, using antiangiogenic drugs to reduce vascular abnormalities or immune-checkpoint inhibitors to improve antiviral defenses, could be of value in COVID-19. However, conflicting data on drug efficacy point to the need for better patient selection and biomarker studies.

INTRODUCTION

A huge international effort has been made in the last 50 years to highlight cancer’s mechanisms of proliferation and dissemination (1). Beyond chemotherapy, new drugs such as targeted therapy, immunotherapy, epigenetic modifiers, and more recently cellular therapies have been approved and have succeeded in improving lifetime expectancy and quality of life of patients living with cancer (2). Apart from their antitumor effects, anticancer drugs also increased knowledge about physiologic pathways in healthy tissues. Outside of cancer indication, some anticancer agents were then developed in extended indications. For example, JAK inhibitors, first approved to treat myeloproliferative neoplasia with activating JAK2 mutations, have now extended indications in rheumatologic diseases and are under development for several dysimmune diseases.

At the end of 2019, the world was destabilized by the emergence of a new coronavirus called SARS-CoV-2 and the coronavirus disease 2019 (COVID-19) pandemic (3). International relationships were greatly affected by the virus dissemination and government interventions to limit its spread (4, 5). A huge effort by the scientific and biomedical community has sought to understand the pathophysiology and clinical manifestations of COVID-19. The full RNA sequence of the new coronavirus was identified with unprecedented speed, and insights into how it interacts with human cells quickly followed (6–8). Concomitantly, clinical studies worldwide revealed the different clinical aspects of severe COVID-19 manifestations characterized by brutal cytokine release syndrome (CRS) and visceral inflammatory involvement, particularly pneumonia (9).

The main risk factors for developing severe COVID-19 are age, male sex, obesity, cardiovascular comorbidities, and diabetes (9, 10). Laboratory science has shown that severe COVID-19 infection is driven mainly by immunopathologic inflammatory pathways mediated by IL6, IL8, tumor necrosis factor alpha (TNFα), and IFNγ (8). Large clinical trials have since evaluated antiviral drugs such as remdesivir (11), anticytokine approaches with anti-IL6 (12) and dexamethasone (13), and passive immunotherapy such as patient convalescent plasmatherapy or recombinant cocktail antibodies against anti-spike antibody (14).

COVID-19 Pathologic Mechanisms

COVID-19 is a human infectious and inflammatory disease related to SARS-CoV-2 infection. A large number of individuals infected with SARS-CoV-2 do not develop symptoms or develop mild manifestations characteristic of flu-like disease.
syndrome and acquired immunity directed against the new betacoronavirus (15). However, about 10% to 15% of patients progress to severe pneumonia and respiratory distress and eventually require admission in the intensive care unit (ICU). Nearly 25% to 30% of patients admitted to the ICU will ultimately die. After an incubation phase and 7 to 10 days of symptoms, a sudden viral pneumonia characterized by profound hypoxemia and interstitial lung disease may occur, related not only to virus infection but also to cytokine storm and immunothrombosis phenomenon (15).

Angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease TMPRSS2, expressed by human alveolar and endothelial cells, participate in the virus cell internalization and activate the spike (S) protein of SARS-CoV-2 into the human cells (16). Obesity is associated with ACE2 and TMPRSS2 overexpression at the surface of endothelial cells through dysregulation of the leptin pathway (17). Also, TMPRSS2 is an androgen-regulated protein, which could explain male sex predisposition to develop severe forms of COVID-19 (18). *Primum movens* to severe COVID-19 seems to be the immunothrombosis phenomenon, characterized by small blood vessel thrombosis associated with microangiopathy and inflammatory infiltration in alveolar capillary, which leads to alveolar edema and associated systemic cytokine storm (19, 20). Patients with severe COVID-19 develop an inflammatory state characterized by increased concentrations of plasmatic cytokines, chemokines, and alarmins related to activation and recruitment of inflammatory cells, such as IL1β, IL6, IL8, TNF, granulocyte-colony stimulating factor, chemokine ligand 2, and calprotectin (S100A8 and S100A9; refs. 21, 22). The most severe COVID-19 infections correlate with low type 1 IFN concentration in blood and transcriptional signature in peripheral blood mononuclear cells (23). Defects in type 1 IFN can be related to functional genetic polymorphisms or autoimmunity directed against type 1 IFN (24, 25). Besides soluble inflammatory and immune factors, patients who develop the most severe forms of COVID-19 present with pathologic hematologic and immunologic features, such as increased neutrophilia, monocytopenia (with loss of nonconventional monocytes), and lymphocytopenia (22, 26). Patients with severe COVID-19 have profound lymphocytopenia with low, but activated and exhausted, CD4+ and CD8+ T cells such as CD19+ B cells and particularly early plasmablasts, which do not succeed in establishing effective antiviral immunity (27–29). Finally, patients with severe COVID-19 are also characterized in their blood and lungs by an emergency myelopoiesis with immature neutrophils and monocytes with deleterious proinflammatory and immunosuppressive function, which can limit the development of effective adaptive immunity (22).

Patients living with cancer are exposed to a significantly higher risk of severe SARS-CoV-2 infection and higher risk of death (30). Particularly, patients with hematologic malignancies have a higher mortality rate related to COVID-19 than patients with solid tumors (31, 32). Among patients with cancer, patients with more recent, disseminated, and symptomatic diseases undergoing chemotherapy are generally those with the most severe infections (33). The explanation for these increased risks remains unclear, such as the amplitude of viral load that could independently predict mortality in both patient populations, which certainly reflects that immunosuppression related to cancer predisposes to a more intense viral replication (34). These data provide a basis for priority for COVID-19 vaccination in patients living with cancer (35).

Administration of anticancer treatments is also an important factor that influences the risks of infectivity and severity of COVID-19 (36, 37). Although chemotherapy was shown to be associated with a higher risk of COVID-19 worsening, interestingly, patients treated with immune-checkpoint immunotherapies or targeted anticancer therapies were not at higher risk (33, 34, 36–38). Other studies suggested that patients treated for cancer and receiving antiandrogenic treatments or antiangiogenic drugs could have improved outcomes (39–41). As these treatments do not seem to increase COVID-19 severity and might improve outcomes for patients, the discussion of repurposing anticancer drugs for COVID-19 began (Fig. 1). Anticancer drugs currently undergoing investigation in clinical trials for the treatment of COVID-19 are depicted in Table 1.

**REPURPOSING DRUGS FROM ONCOLOGY**

### Anti-Inflammatory Drugs

**Dexamethasone**

Corticosteroids, in particular dexamethasone, are drugs commonly used to treat hematologic malignancies such as multiple myeloma, non-Hodgkin lymphoma, or acute lymphoblastic leukemia. For the treatment of severe COVID-19 with viral pneumonia, the British Recovery study has shown that dexamethasone improves the overall survival of patients needing respiratory support (either invasive mechanical ventilation or oxygen alone; ref. 13). Dexamethasone then became the standard of care for patients hospitalized with COVID-19 with viral pneumonia requiring oxygen support.

Other anti-inflammatory drugs targeting new molecular pathways may be tested for patients with severe COVID-19. Biological studies have shown that calprotectin is one of the key molecules implicated in the inflammatory cascade leading to severe forms of COVID-19 (22), suggesting calprotectin as a potential new therapeutic target.

**Anti–Cytokine IL6**

In hematologic oncology, CRS is known as a frequent complication associated with chimeric antigen receptor-T (CAR-T) cells or bispecific antitumor antibodies. CRS is characterized by fever, hypotension, and eventually hypoxemia or biological abnormalities including coagulopathy (42), related to a sudden release of cytokines by the immune system when the latter encounters the tumor antigen under the effect of anticancer treatment (43). CRS is dominated by high levels of IL6 in serum, which led to anti-IL6 receptor therapies being proposed to control CRS (43). The respiratory distress and high fever during COVID-19 viral pneumonia may share similarities with CRS (44).

The cytokine storm induced by the SARS-CoV-2 virus is becoming better understood. Cytokines such as IL6, IL10, and TNFα, and the overactivation of the systemic complement pathways, namely substrates C5b-9 and C4d, are correlated with the severity of COVID-19 (45). This systemic inflammation and complement activation are also associated with the phenomenon of immunothrombosis, a hypercoagulopathy
Figure 1. Anticancer drugs proposed for drug repurposing in COVID-19 infection and presented according to their potential therapeutic targets. In mild to moderate COVID-19, anti–PD-1 reinforces the T-cell immune system and may improve viral clearance. Antiandrogen drugs block the TMPRSS2 receptor used by the virus for entry into the cell. In severe COVID-19, JAK/STAT or BTK inhibitors mitigate the inflammatory signaling cascade into the cell and help control the cytokine storm. Anticytokines (anti-IL6 receptor) directly reduce the cytokine storm by blocking the IL6 receptor on the cell surface. Antiangiogenic drugs could limit vascular abnormalities induced by the virus in endothelium. Other anticancer drugs, such as plitidepsin and apilimod, have antiviral activity against SARS-CoV-2 by targeting the host protein eEF1A or by affecting endosomal homeostasis, respectively.

state affecting up to 16% of patients hospitalized for COVID-19 (46). Dysregulated neutrophil extracellular traps in the endothelium of patients also contribute to immunothrombosis in patients with severe COVID-19, by propagating inflammation and microvascular thrombosis (46).

Several anticytokine therapeutics aiming to curb COVID-19–related cytokine storm have been investigated. Retrospective studies and randomized clinical trials evaluating the most used anti-IL6 receptor blocker tocilizumab antibody suggested a therapeutic effect of the drug (47–49), while other clinical trials failed to complete their efficacy endpoints (50–52). Overall, the results of additional clinical trials with longer follow-up of enrolled patients are needed to better understand the magnitude of the therapeutic effect of anti-IL6 receptor therapy in patients with COVID-19. A more precise, and probably more selective, definition of the patient population with COVID-19 who may or may not benefit from anti-IL6 receptor therapy remains to be clarified in future studies.

**Targeting the BTK Signaling Pathway**

Bruton tyrosine kinase (BTK) inhibitors are approved therapies for treating lymphoid blood disorders such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), or Waldenstrom disease (53). The SARS-CoV-2 virus can generate an overactivation of immune cells, including both B and T cells, leading to a “cytokine storm,” thus contributing to acute lung injury and respiratory distress (21). BTK pathway effector molecules contribute to the cytokine storm and are potential targets for the drug therapy of COVID-19 (41). An observational study evaluating the use of acalabrutinib in 19 patients with COVID-19 hospitalized and requiring oxygen supplementation suggested potential efficacy. However, the BTK inhibition hypothesis must be interpreted with caution, because of the concomitant use of dexamethasone in initial studies. Definitive results of a randomized controlled clinical trial investigating acalabrutinib for patients with COVID-19 (CALAVI phase II trial: NCT04380688 and NCT04346199) are pending, but a recent press communication reported that the study did not reach its primary endpoint as compared with best supportive care alone.

**Implications of JAK/STAT Inhibitors to Treat COVID-19**

JAK is a family of intracellular, non–receptor tyrosine kinases that transduce signals transferred by the cytokines...
Table 1. Examples of cancer drugs currently tested for COVID-19

<table>
<thead>
<tr>
<th>Targeted pathway</th>
<th>Drug</th>
<th>MoA related to Covid pathogenesis</th>
<th>COVID-19 severity</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticytokines</td>
<td></td>
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<tr>
<td>IL6</td>
<td>Tocilizumab</td>
<td>Prevents the “cytokine storm”</td>
<td>Severe</td>
<td>NCT04377659 (Phase II)</td>
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<td>NCT04363853 (Phase II)</td>
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<td></td>
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<td>Requiring hospitalization</td>
<td>NCT04317092 (TOCIVID-19)</td>
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<td></td>
<td>NCT04372186 (EMPACTA) (Phase III)</td>
</tr>
<tr>
<td>IL8</td>
<td>BMS-986253</td>
<td>Prevents the “cytokine storm”</td>
<td>Severe</td>
<td>NCT04347226 (Phase II)</td>
</tr>
<tr>
<td>JAK inhibitors</td>
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<tr>
<td>Pacritinib (JAK2i)</td>
<td>Blocks multiple, proinflammatory cytokines; antiviral effects by impeding cellular viral endocytosis</td>
<td>Severe</td>
<td>NCT04404361 (PRE-VENT) (Phase III)</td>
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</tr>
<tr>
<td>Baricitinib (JAK1/2i) + antiviral therapy</td>
<td>Moderate and severe</td>
<td>NCT04373044 (Phase II)</td>
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<tr>
<td>Baricitinib</td>
<td></td>
<td></td>
<td>Moderate and severe</td>
<td>NCT04346147 (Phase II)</td>
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<td>NCT04390464 (Phase IV)</td>
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<tr>
<td>Ruxolitinib (JAK1/2i)</td>
<td>Severe</td>
<td>NCT04331665 (Phase II)</td>
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<tr>
<td>BTK</td>
<td>Ibrutinib</td>
<td>Abrogation of pulmonary inflammatory cytokines, lung injury</td>
<td>Requiring hospitalization</td>
<td>NCT04439006 (Phase II)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04375397 (INSPIRE) (Phase II)</td>
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<td>NCT04346199 (CALAVI) (Phase II)</td>
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<tr>
<td>Acalabrutinib</td>
<td></td>
<td></td>
<td>Requiring hospitalization</td>
<td>NCT04419623 (Phase I/II)</td>
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<tr>
<td>TL-895</td>
<td></td>
<td></td>
<td>Requiring hospitalization</td>
<td>NCT04344782 (CORIMMONO-BEVA) (Phase II)</td>
</tr>
<tr>
<td>Antiangiogenics</td>
<td>Bevacizumab</td>
<td>Inhibits VEGF, a key factor to increase vascular permeability and induce pulmonary edema caused by inflammatory exudation in COVID-19 infection</td>
<td>Severe</td>
<td>NCT04305106 (BEST-RCT) (Phase II)</td>
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<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04275414 (BEST-CP) (Phase II)</td>
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<td></td>
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<td>Requiring more than 3 L of oxygen</td>
<td>NCT04344782 (CORIMMONO-BEVA) (Phase II)</td>
</tr>
<tr>
<td>Androgen blockade</td>
<td>Bicalutamide</td>
<td>Blocks TMPRSS2</td>
<td>Mild/moderate COVID-19 requiring hospitalization</td>
<td>NCT04374279 (RECOVER) (Phase II)</td>
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<td></td>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>NCT04509999 (Phase III)</td>
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<tr>
<td></td>
<td>Degarelix</td>
<td>Suppresses androgens, which might regulate TMPRSS2 expression in lung tissue</td>
<td>Veterans hospitalized for COVID-19 (severity 3, 4, 5 on the influenza scale)</td>
<td>NCT04397718 (HITCH) (Phase II)</td>
</tr>
<tr>
<td></td>
<td>Enzalutamide</td>
<td>Antiandrogen inhibiting the expression of androgen-regulated proteins, such as TMPRSS2</td>
<td>High-risk male COVID-19 patients, mild symptoms, not requiring hospitalization</td>
<td>NCT04456049 (Phase II)</td>
</tr>
<tr>
<td>Other</td>
<td>IFNα</td>
<td>Abrogates type I IFN deficiency in severe COVID-19</td>
<td>Severe</td>
<td>NCT04534725 (C-SMART)</td>
</tr>
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<td></td>
<td>IMM-101</td>
<td>Stimulates dendritic cells</td>
<td>Prevention of severe COVID-19</td>
<td>NCT04442048 (COV-IMMUNO)</td>
</tr>
</tbody>
</table>
### Table 1. Examples of cancer drugs currently tested for COVID-19 (Continued)

<table>
<thead>
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<th>COVID-19 severity</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cells</td>
<td>FT516</td>
<td>Engineered NK cells expressing CD16, which destroy antibody-coated target cells</td>
<td>Hospitalized COVID-19 patients with hypoxia</td>
<td>NCT04363346 Phase I</td>
</tr>
<tr>
<td>Double-stranded RNA</td>
<td>Rintatolimod ± IFN alpha</td>
<td>Mimics viral infection, stimulates the immune system to limit viral replication</td>
<td>Mild/moderate</td>
<td>NCT04379518 Phase I/II</td>
</tr>
<tr>
<td>PI3K–AKT</td>
<td>Duvelisib (PI3K inhibitor)</td>
<td>Inhibits aberrant hyperactivation of the innate immune system</td>
<td>Severe</td>
<td>NCT04487886 (DAMPEN-CI) Phase II</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04372602 Phase II</td>
</tr>
<tr>
<td>MAPKAPK2 (MK2) inhibitor</td>
<td>(ATI)-450</td>
<td>Inhibits multiple inflammatory cytokines</td>
<td>Moderate or severe</td>
<td>NCT04481685 Phase II</td>
</tr>
<tr>
<td>HSP</td>
<td>MPT0B640 (HSP inhibitor)</td>
<td>Inhibits defective HSP in COVID-19, to avoid the “cytokine storm”</td>
<td>Requiring hospitalization</td>
<td>NCT04526717 Phase I</td>
</tr>
<tr>
<td>SK2</td>
<td>Opanib (SK2-selective inhibitor)</td>
<td>Anti-inflammatory and antiviral activity</td>
<td>Requiring supplemental oxygen at baseline</td>
<td>NCT04414618 Phase II</td>
</tr>
<tr>
<td>Nucleo-cytoplasmic transport inhibitor</td>
<td>Selinexor (selective inhibitor of XPO1)</td>
<td>Anti-inflammatory activity, reduction of proinflammatory cytokines levels</td>
<td>Severe</td>
<td>NCT04534725 (C-SMART) Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04349098 Phase II</td>
</tr>
<tr>
<td>SUMO</td>
<td>TAK-981</td>
<td>Inhibits SUMOylation, a process involved in the post-translational modification of the coronavirus N protein</td>
<td>Moderately severe</td>
<td>NCT03648372 Phase I</td>
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<tr>
<td>eEF1A inhibition</td>
<td>Plitidepsin</td>
<td>Antiviral activity by the inhibition of eEF1A, identified in SARS-CoV-2 virions</td>
<td>Requiring hospitalization</td>
<td>NCT04382066 (APLICOV-PC) Phase I</td>
</tr>
<tr>
<td>eEF4A inhibition</td>
<td>Zotatifin</td>
<td>Antiviral activity by impairing the cap-dependent mRNA translation of SARS-CoV-2</td>
<td>Mild or moderate</td>
<td>NCT04632381 (PROPEL-PC) Phase I</td>
</tr>
<tr>
<td>CK2 inhibition</td>
<td>Silmitasertib</td>
<td>Antiviral activity by inhibiting CK2, involved in viral replication and virus-induced cytoskeleton organization</td>
<td>Moderate</td>
<td>NCT04663737 Phase II</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04668209 Phase II</td>
</tr>
</tbody>
</table>

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CK2, casein kinase 2; eEF1A, Eukaryotic translation elongation factor 1 alpha 1; GM-CSF, granulocyte macrophage–colony stimulating factor; HSP, heat shock protein; IFN, interferon; MoA, mechanism of action; MoAb, monoclonal antibody; NFkB, nuclear factor kB; NK, natural killer; SK2, sphingosine kinase-2; TMPRSS2, transmembrane protease, serine 2; VEGF, vascular endothelial growth factor.

via the JAK–STAT signaling pathway. The JAK–STAT pathway is overactivated by activating mutations in JAK2 hematologic malignancies (54) such as myeloproliferative syndromes including myelofibrosis or polycythemia vera. The JAK–STAT pathway was recently highlighted as an important inflammatory signaling pathway in inflammatory diseases, and JAK inhibitors are approved drugs in rheumatoid arthritis. JAK inhibitors are expected to reduce cytokine storms (55); therefore, they were suggested as a promising therapy to mitigate the inflammatory cascade generated by COVID-19 (56). Preclinical studies in humans suggest that JAK inhibitors may restrict the expression of the ACE2 receptor—necessary for the entry of the SARS-CoV-2 virus—into human cells (57, 58). A clinical study of 601 patients suggests that baricitinib, a JAK1/2 inhibitor, could improve the outcome of patients with severe COVID-19, primarily by reducing the rampant immune inflammation (58). A double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with COVID-19 concluded that baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19 (59). Data from
randomized trials with a JAK inhibitor alone versus placebo for the treatment of COVID-19 are still pending (Table 1), while one trial was terminated early for futility (NCT04377620). In light of the hypercoagulability state of COVID-19, vigilance is recommended given the potentially increased risk of thrombosis reported with some JAK inhibitors (60).

**Antiangiogenics**

The immunothrombosis phenomenon is associated with upregulation of macrophages, complement substrates, platelet activation, thrombosis, and proinflammatory markers (61, 62). Moreover, proangiogenic factors, such as VEGF and angiopoietin 2, are crucial factors implicated in vascular permeability and pulmonary edema of patients with COVID-19 (63). In an autopsy study performed on lungs from people who died from viral infections, the amount of new vessel growth associated with COVID-19 was 2.7 times higher compared with that found in patients with H1N1 influenza virus. Pathologic findings in patients with COVID-19 indicate severe endothelial injury, disruptive cell membranes, and widespread thrombosis (20). In severe forms of COVID-19, some researchers suggest antiangiogenic drugs may suppress pulmonary edema by inhibiting proangiogenic factors and by promoting a vascular normalization. In a single-arm trial investigating bevacizumab plus standard of care in 26 patients with severe COVID-19 infection (NCT04275414), a single dose of 7.5 mg/kg of bevacizumab was associated with rapid improvement in PaO2/FiO2 ratios, improved oxygen support status in 92% of patients by day 28 (versus 62% in the external comparison cohort treated with standard of care only), and significant radiologic reduction of pneumonia lesions within seven days. Of note, no drug-related serious adverse effects were reported (64). However, in this study, patients were excluded if they had received full-dose anticoagulant within 10 days before enrollment or had thrombosis within 6 months before enrollment, criteria that apply to a significant proportion of patients with cancer. Other ongoing clinical trials are investigating bevacizumab, and results are pending (Table 1). A clinical trial (NCT04342897) evaluating the effect of targeting angiopoietin 2 in patients with COVID-19 was terminated early for futility. Further trials evaluating antiangiogenics should carefully assess the risk of thrombosis and possibly offer concomitant anticoagulation treatments to control this risk of thrombosis.

**Immune-Checkpoint Blockade**

An effective immune response against viral infections depends on the activation of host CD8\(^+\) T cells expected to eliminate cells containing the SARS-CoV-2 virus (65, 66). In patients with severe COVID-19, there is a reduced number of CD4\(^+\) and CD8\(^+\) T cells, while the surviving T cells exhibit an exhausted phenotype, with a higher level of PD-1 expression (67, 68). The reduced T-cell counts (total T cells < 800/\(\mu\)L, CD8\(^+\) cells < 300/\(\mu\)L and CD4\(^+\) cells < 400/\(\mu\)L) in the blood of patients with COVID-19 were negatively correlated with the levels of TNF\(\alpha\), IL6, and IL10 (68). In an observational clinical study of 113 patients with cancer and laboratory confirmed COVID-19 while on treatment with immune-checkpoint inhibitors (ICI) without chemotherapy, the mortality by COVID-19 in patients under ICI did not seem to be higher compared with rates reported in the general cancer population (69). Another observational study conducted in 178 patients with cancer managed for COVID-19 did not identify increased risk of clinical worsening or death in patients treated with ICI for cancer. Conversely, patients receiving cytotoxic chemotherapy had an increased risk of clinical worsening and death in the univariable analysis and a trend toward a higher risk of death in the multivariable analysis, after adjusting for ECOG performance status and cancer status (33). Similarly, chemotherapy negatively affected survival outcomes in patients with thoracic cancer and COVID-19 in the TERAVolt cohort, as opposed to immunotherapy and targeted therapy (70, 71). However, in another observational study including 423 patients with cancer with symptomatic COVID-19, treatment with ICI \((N = 31)\) was a predictor for hospitalization and severe disease, while treatment with chemotherapy was not (72). Overall, these data are limited and their conflicting interpretation imposes caution about potential interest in repurposing ICI for COVID-19. ICI might have a dual effect: it might enhance T cell–mediated viral clearance in the early phase, but it has been suggested to also facilitate late-inflammatory states by promoting T regulatory cell activation and the exacerbation of the cytokine storm (73, 74). The sum of these data suggests that future trials evaluating the potential interest of ICI for COVID-19 should select the patient population to be treated, most likely considering treatment in the early phase of the disease and without a cytokine storm.

**Antiandrogenic Treatment**

SARS-CoV-2 virus harnesses the TMPRSS2 receptors to enter within the host human cell, and these receptors are regulated by the androgen receptor (16). The TMPRSS2 gene is strongly upregulated in prostate cancer cells, and it has a testosterone-activated response element, suggesting potential antiandrogenic treatment in patients with COVID-19. In a cohort of men with prostate cancer, COVID-19 infection was less likely to be reported in patients treated with androgen deprivation therapy (ADT) as compared with those without (ADT 4/5,273 cases versus 114/37, odds ratio 4.05, 95% confidence interval 1.55–10.59, \(P = 0.00043\); ref. 39). However, ADT effect seems to be modest, as the number of patients needed to treat with ADT for the prevention of one case of COVID-19 was 434. This minimal potential therapeutic effect makes ADT a less appealing option in the case of patients without prostate cancer, also considering the associated side effects of ADT (75). Moreover, preliminary data from multicenter registries do not support a decrease in COVID-related mortality with antiandrogenic drugs (76). Ongoing trials testing bicalutamide, enzalutamide, or GnRH antagonists are ongoing (Table 1). Also, camostat mesylate, a direct TMPRSS2 inhibitor, is currently being investigated in several clinical trials for COVID-19 as monotherapy or in combination with bicalutamide, with the aim of reducing the SARS-CoV-2 viral burden and forestalling complications of COVID-19 (NCT0435328, NCT04583592, NCT04608266, NCT04524663, and NCT04652765).
The Targeting of Host-Interacting Proteins and Kinases Dysregulated during Infection

Recent preclinical studies on SARS-CoV-2–infected cells found important interactions between human proteins and SARS-CoV-2, and a dramatic rewiring of phosphorylation on host and viral proteins, highlighting how the virus uses the host’s posttranslational regulatory systems to induce rapid signaling changes (77–79). The mapping of proteomic changes to pharmacologic modulators identified promising target–drug pairs that might trigger robust antiviral effects (77, 78). For instance, eEF1A was identified in SARS-CoV virions (80, 81), and plitidepsin, an eEF1A inhibitor approved in Australia for the treatment of multiple myeloma, was shown to have a potent anti–SARS-CoV-2 antiviral activity in preclinical studies (IC90 = 0.88 nmol/L; ref. 81). Plitidepsin was 27.5-fold more potent than remdesivir in vitro, while having limited toxicity (81). These data indicated promising therapeutic repurposing for plitidepsin as antiviral therapy for COVID-19, and phase II/III trials are pending.

Another target is the virus-induced upregulation of casein kinase 2 (CK2), which might facilitate cell-to-cell spread by driving actin polymerization. CK2 inhibition with silmitasertib, currently being tested in recurrent medulloblastoma (NCT03904862), showed robust antiviral activity in SARS-CoV-2–infected cells (77). Phosphatidylinositol-3-Phosphate/Phosphatidylinositol-5-Kinase (PIKfyve) is a protein that resides in early endosomes, being involved in endomembrane homeostasis. Its inhibition has the potential to inhibit viral entry, making it a promising target for the treatment of early COVID-19 infection. In vitro experiments showed that apilimod, a specific PIKfyve kinase inhibitor investigated in early-phase clinical trials for the treatment of non-Hodgkin lymphoma, successfully inhibited viral replication during entry (82). Apilimod is currently being evaluated for its impact on SARS-CoV-2 viral load in patients with confirmed COVID-19 infection treated in an outpatient setting (NCT04446377). SARS-CoV-2 also increases phosphatidylinositol 5-kinase during entry (77). Other examples of promising target–drug pairs include AXL and gilteritinib (approved by the FDA for relapsed or refractory acute myeloid leukemia with FLT3 mutations) or p38 and p38 inhibitors, such as ralmitinib (undergoing development in ovarian cancer; ref. 77).

CONCLUSION

A better understanding of molecular mechanisms associated with COVID-19 as well as clinical observations from patients with COVID-19 concomitantly treated for cancer generates various hypotheses concerning potential anticancer drug repositioning. Although strong clinical evidence is still lacking, the sum of these data suggests anticancer drugs could be regarded as potent antiviral therapies, with both direct antiviral effects and indirect effects by blocking signaling pathways such as JAK/STAT or abnormal angiogenesis. Clinical trials for hypothesis testing of anticancer drugs are an encouraging strategy for discovering new possible therapies for COVID-19.
Anticancer Drug Repurposing in COVID-19


Repurposing of Anticancer Drugs Expands Possibilities for Antiviral and Anti-Inflammatory Discovery in COVID-19

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