

JAK Inhibition as a New Treatment Strategy for Patients with COVID-19

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Keywords

Bricitinib · JAK-STAT pathway · JAK inhibitors · Methotrexate · Cytokine · Angiotensin-converting enzyme inhibitor · Angiotensin receptor blocker

Abstract

After the advent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the outbreak of coronavirus disease 2019 (COVID-19) commenced across the world. Understanding the Immunopathogenesis of COVID-19 is essential for interrupting viral infectivity and preventing aberrant immune responses before a vaccine can be developed. In this review, we provide the latest insights into the roles of angiotensin-converting enzyme II (ACE2) and Ang II receptor-1 (AT1-R) in

this disease. Novel therapeutic strategies, including recombinant ACE2, ACE inhibitors, AT1-R blockers, and Ang 1–7 peptides, may prevent or reduce viruses-induced pulmonary, cardiac, and renal injuries. However, more studies are needed to clarify the efficacy of these therapeutics. Furthermore, considering the common role of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway in AT1-R expressed on peripheral tissues and cytokine receptors on the surface of immune cells, potential targeting of this pathway using JAK inhibitors (JAKinibs) is suggested as a promising approach in patients with COVID-19 who are admitted to hospitals. In addition to antiviral therapy, potential ACE2- and AT1-R-inhibiting strategies, and other supportive care, we suggest other potential JAKinibs and novel anti-inflammatory combination therapies that affect

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the JAK-STAT pathway in patients with COVID-19. Since the combination of MTX and baricitinib leads to outstanding clinical outcomes, the addition of baricitinib to MTX might be a potential strategy.

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Background

After the sudden emergence of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19) conquered the world [1]. CoVs are a group of RNA viruses belonging to the Coronaviridae family. SARS-CoV-2 is detected within 1–2 days after the patient's symptoms, reaches a peak 4–6 days later, and is cleared within 18 days [2]. The clinical manifestations of COVID-19 range from asymptomatic to severe infections that require admission to an intensive care unit, with various mild to severe respiratory, gastrointestinal, hepatic, and neurologic involvements [3]. Such a novel virus with a high virulence and mortality necessitates further study to shed light on the immunopathogenesis of COVID-19 for the development of novel antiviral medications or vaccines to make the disease treatable or preventable, respectively.

Angiotensin-Converting Enzyme II

Recently, a critical host susceptibility factor, known as angiotensin-converting enzyme II (ACE2), has been identified for both SARS-CoV (SARS in 2003) and SARS-CoV-2 (COVID-19 in 2019) in humans and animals. It is crucial for entry into target cells with the help of the cellular protease TMPRSS2 [4, 5]. The renin-angiotensin system is a pivotal regulator of blood pressure (Fig. 1) [6]. ACE2, which is highly expressed in the heart, lung, kidneys, brain, testes, liver, and small intestine [7], is a zinc carboxypeptidase and inactivates the potent vasoconstrictive peptide angiotensin II (Ang II) by removing the C-terminal phenylalanine residue to yield heptapeptide Ang [1–7]. This conversion counterbalances the vasopressive function of Ang II [8]. Astonishingly, ACE2 binds to the trimers of spike proteins on the SARS-CoV-2 capsid, which triggers clathrin-dependent concomitant endocytosis of SARS-CoV-2 and ACE2 [9]. Following the interaction of the spike protein and ACE2, a disintegrin and metalloprotease 17 (ADAM17) is activated; consequently, it leads to shed-

ding of ACE2 from the cell surface [10], thereby producing locally increased Ang II and hyaluronan (HA) levels resulting in the development of acute respiratory distress syndrome (ARDS) [11], which is the main cause of death in patients with COVID-19. Therapeutic interventions with soluble ACE2 or anti-ACE2 antibodies may impair the contribution of SARS-CoV-2 and ACE2.

Administration of soluble receptor-binding domain (RBD), the main domain derived from the SARS S-protein that can bind to the ACE2 and contains 193 amino acids, can effectively block the entry of SARS in cell culture. In addition, an antibody that binds to the ACE2 protein can be used to block this receptor. Nevertheless, several issues remain to be taken into consideration before applying these novel strategies, including the dose of administration to saturate ACE2-binding capacity owing to the ubiquitous ACE2 presence throughout the body, turnover or recycling of ACE2 on the surface of target cell, and local or systemic administration. Finally, binding both suggested ACE2 blockers may paradoxically improve or exacerbate the symptoms of the lung injury. Researchers suggest that it should be best administered during the initial phase of infection or as a prophylaxis to inhibit viral entry [12]. As mentioned earlier, recent studies have established that the lung is full of clear jelly-like liquid in COVID-19. Although the nature of the lucid jelly remains to be fully elucidated, HA is one of the components found in this fluid. Inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor- α (TNF- α) strongly induce HA-synthase-2 (HAS2) in the lung's endothelial and epithelial cells, as well as fibroblasts. Whenever breathing becomes difficult, hyaluronidase should be applied intratracheally; meanwhile, hymecromone (4-methylumbelliferone; 4-MU), an inhibitor of HAS2, may be administered to inhibit HAS2 [13].

Angiotensin II Receptors

Two subtypes of G protein-coupled receptors exist through which Ang II exerts its action, i.e., the Ang II type 1 receptor (AT1-R) and Ang II type 2 receptor (AT2-R) (Fig. 1). Most of the cardiovascular/renal-related functions of Ang II are generally attributed to AT1-R. The expression of AT2-R is high in the developing fetus, while it is expressed at very low levels in the adult cardiovascular system. Angiotensin II receptor blockers (ARBs) (losartan, valsartan, telmisartan, and

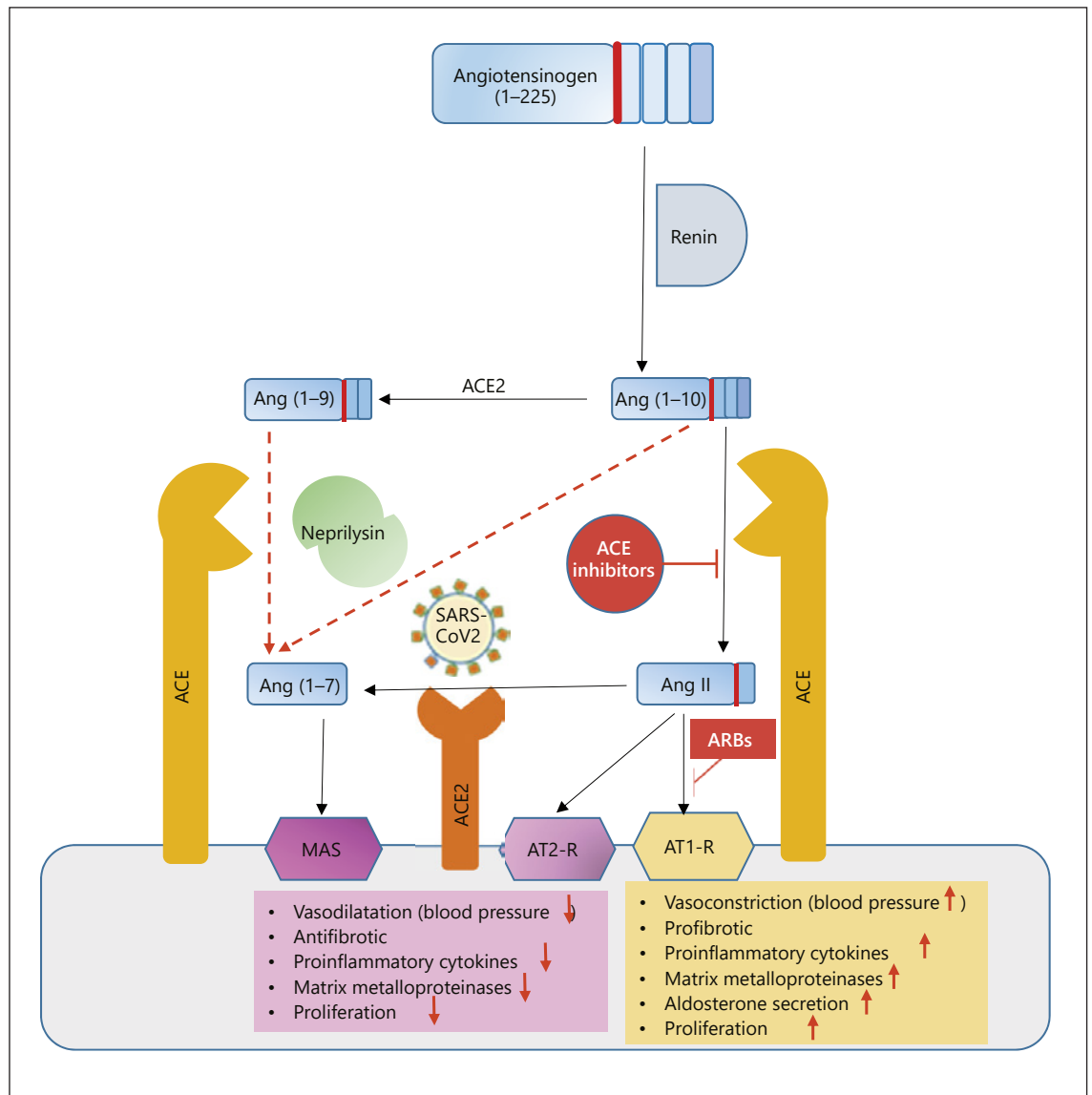


Fig. 1. The renin-angiotensin system is a pivotal regulator of hypertension, which controls the homeostasis of main electrolytes and body fluids. It starts with liver synthesis of the angiotensin (Ang) peptide precursor, named angiotensinogen. Subsequently, the potent vasoconstrictive peptide Ang II is cleaved by ACE, which increases blood pressure through the activation of Ang II type 1 (AT1R). In contrast, ACE2 inactivates Ang II by removing

the C-terminal phenyl alanine residue to yield heptapeptide Ang (1-7), which exerts its opposing effects through the Mas receptor. Ang I is also cleaved to Ang (1-7) and Ang (1-9) by the action of neprilysin and ACE2, respectively. Then, Ang-1-9 is cleaved with the help of either NEP or ACE to produce Ang-1-7 in a minor pathway. Higher levels of Ang (1-7) originate from Ang II rather than Ang I and Ang (1-9).

candesartan) are suggested for the treatment of COVID-19; however, contradictory outcomes have been reported so far. There are paradoxical and limited reports on ACE inhibitors (captopril and enalapril) and ARBs in patients with COVID-19 either to confirm or to prohibit the use of these therapeutics. Moreover, ACE2

may play beneficial rather than detrimental roles in patients with lung injury. In addition, a recent study indicated that elderly (age >65 years) patients with COVID-19 accompanied by hypertension comorbidity who are taking antihypertensive ARBs may be less likely to develop severe lung disease [14]. Innovative approach-

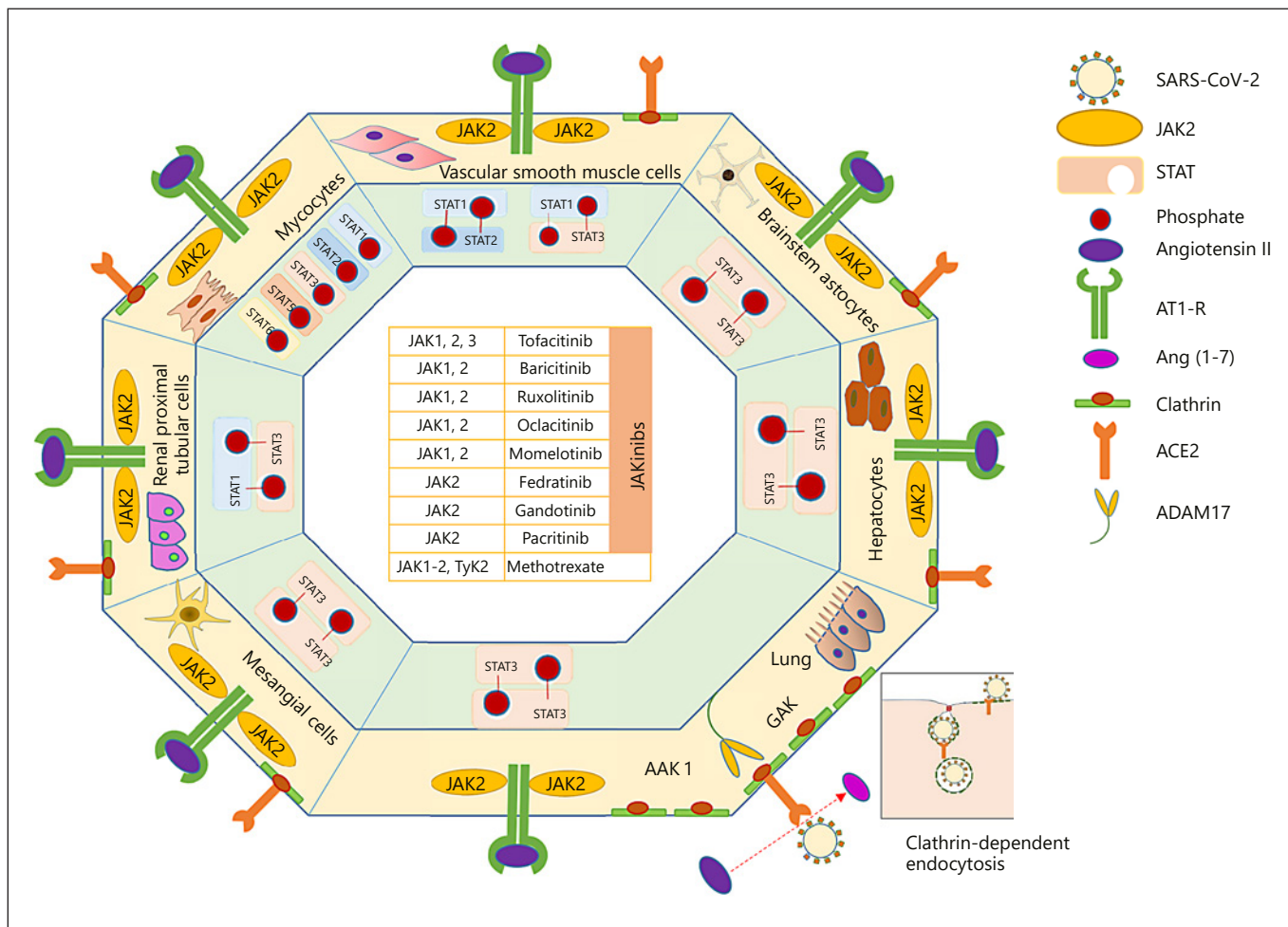


Fig. 2. Target cells potentially infected with SARS-CoV-2 in COVID-19.

es, such as recombinant ACE2, ACE inhibitors, ARBs, and Ang 1–7 peptides, as well as likely aldosterone synthase inhibitors, may prevent or reduce virus-induced pulmonary or cardiac damage. However, withdrawal of these inhibitors may be harmful in some high-risk patients with proven or suspected COVID-19. Consistent with the present guidelines, patients with hypertension or chronic kidney disease should keep taking antihypertensive drugs as administered by the physician without interruption because this action increases the readmission probability to hospitals and mortality rates in patients with heart and kidney failure [15, 16]. Considering the equal efficacy but much lower side effects, ARBs may be used more favorably in patients who are at a higher risk of developing severe COVID-19.

AT1-R and Cytokine Signaling through the Janus Kinase-Signal Transducer and Activator of Transcription Pathway in COVID-19

Of note, Ang II mediates its actions through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway, leading to vasoconstriction, hypertension, and chronic tissue injury [17]. The JAK-STAT pathway is involved in orchestrating the immune system to play a coordinated symphony. There are 4 mammalian proteins that belong to the nonreceptor JAK family, i.e., JAK1, JAK2, JAK3, and Tyk2. JAK1–2 and TYK2 are found ubiquitously, whereas JAK3 seems to act in hematopoietic lineage and exerts critical roles in lymphocyte function. In addition, human STAT family is comprised of 7 STAT, i.e., STAT1, STAT2, STAT3,

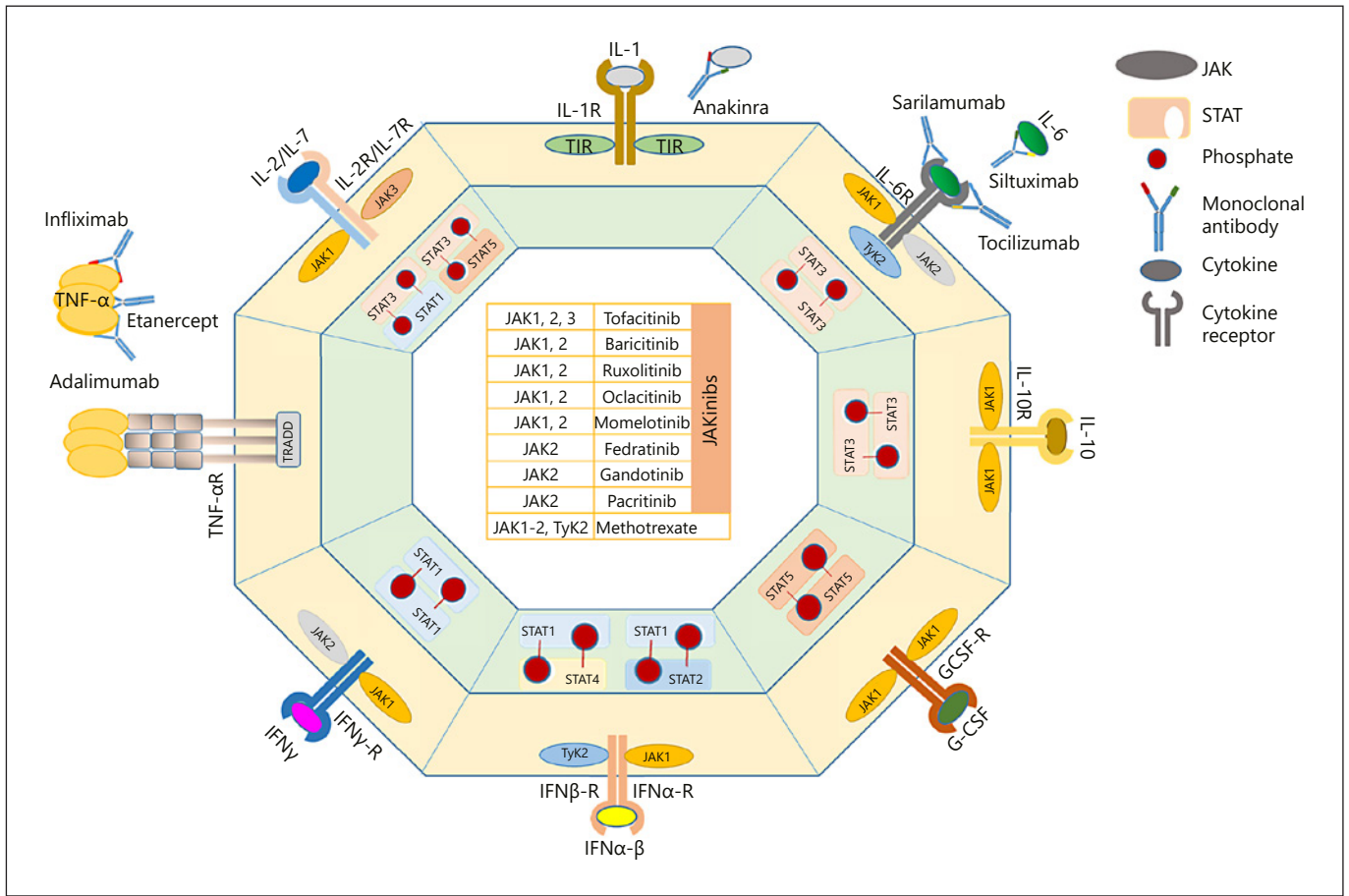


Fig. 3. Cytokines and cytokine receptors participating in the COVID-19 immunopathogenesis. G-CSF, granulocyte colony stimulating factor.

STAT4, STAT5A, STAT5B, and STAT6 [18]. The renin-angiotensin system and proinflammatory cytokines have reciprocal relationships. Indeed, Ang II augments the infiltration of immune cells which, in turn, increases the local production of proinflammatory cytokines such as TNF- α , IL-1, IL-6, and interferon (IFN)- γ in target tissues [19]. Ang II signaling can be mediated through the JAK-STAT pathway in the cardiovascular system, renal proximal tubular cells, mesangial cells, brainstem astrocytes, and hepatocytes (Fig. 2). To this end, AT1-R recruits and phosphorylates JAK2 and, based on the target cell, one of the STAT is phosphorylated by activated JAK2. On the other hand, another mechanism suggested for a subgroup of patients with severe COVID-19 developing ARDS may be a cytokine storm, which is defined as the release of high concentrations of proinflammatory cytokines, including IL-1, IL-2, IL-6, IL-7, IL-10, TNF- α (Fig. 3), granulocyte-colony stimulating factor, interferon (IFN)- γ inducible

protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein 1- α (MIP1- α) by immune cells. The cytokine storm initiates a fulminant response by the immune system, leading to multiple organ failure and even death in severe COVID-19 [20]. Accordingly, since not only AT1-R but also a lot of cytokine receptors use this pathway for signal transduction, targeting the JAK-STAT pathway may provide a new avenue toward the management of COVID-19 before a vaccine can be developed.

JAK Inhibitors

JAK inhibitors (JAKinibs) are biologic agents that inhibit type I/II cytokine receptors. They are currently being used for the treatment of some diseases, and second-generation selective Jakinibs are being designed and in-

vestigated [21]. Tofacitinib is an effective oral JAK2/1/3 inhibitor that was approved by the FDA for the treatment of rheumatoid arthritis (RA) in 2012 (Fig. 2, 3) [18]. Since JAK3 is limited to cytokines using the common γ chain family, tofacitinib can effectively block IL-2, IL-7, and IL-6. However, herpes zoster and cellulitis infections may occur. Both low-density lipoprotein and high-density lipoprotein levels increase while blood neutrophils are decreased. In a study in patients with RA it decreased erythrocyte sedimentation rates and C-reactive protein levels [19]. Nevertheless, no treatment of COVID-19 with tofacitinib has been reported to date. Baricitinib is a selective JAK1/JAK2 inhibitor approved for the treatment of RA [18]. Both SARS-CoV-2 host cells (using AT1-R) and a large number of immune cells (using cytokine receptors) employ JAK2 for signal transduction through the JAK-STAT signaling pathway, and thus finding suitable and efficient JAKinibs or other immunosuppressive drugs may improve the treatment of COVID-19 (Fig. 2, 3). In this regard, the latest studies show that baricitinib is a potential treatment for ARDS in COVID-19. Furthermore, it can decrease the virus infectivity for lung cells. The ACE2 receptor has several regulators among which AP2-associated protein kinase-1 (AAK1) and cyclin G-associated kinase (GAK) mediate clathrin-dependent endocytosis (Fig. 2). Baricitinib not only interrupts the passage and intracellular assembly of SARS-CoV-2 into the target cells via disruption of AAK1 signaling but it also reduces the inflammation in patients with ARDS [22]. Although in a study in patients with RA who showed an inadequate response to prior methotrexate (MTX) treatment a dose-dependent decrease in hemoglobin levels was evident [23], a decrease in neutrophil counts together with an increase in low-density lipoprotein and high-density lipoprotein levels was observed in another study in patients with refractory RA following the use of baricitinib [24]. In contrast, tofacitinib does not significantly inhibit AAK1 [25]. Stebbing et al. [26] revealed that 3 JAKinibs, including baricitinib, ruxolitinib, and fedratinib, had similar JAK inhibitor potencies, while the high affinity of baricitinib to AAK1 and the merit of its once-daily oral dosing made it the best of these JAKinibs. Contrary to the other antiarthritic drugs or JAK inhibitors, baricitinib can inhibit clathrin-dependent endocytosis. Although JAK inhibition may weaken host inflammatory responses and impair hematopoiesis somehow, combination therapy using baricitinib and direct-acting antivirals, including lopinavir or ritonavir and remdesivir, can decrease viral infection and amplification, as well as unwanted host inflammatory reactions

[26]. Trials in human lupus have been initiated using baricitinib with a dose of 4 mg daily, with improved clinical symptoms. Several trials, including phase 3 trials, have been completed for many disorders such as psoriasis, alopecia areata, allergic dermatitis, dermatomyositis, and graft-versus-host disease (GVHD) [27]. Other JAKinibs such as ruxolitinib, memolitinib, and oclacitinib target both JAK1 and JAK2 which can potentially affect signaling pathways downstream of the receptors involved in COVID-19 development (Fig. 2, 3). Fedratinib and pacritinib are other JAK2 inhibitors, and clinical trials are ongoing for the treatment of myelofibrosis. Pardanani et al. [28], who conducted a phase 1 trial in 59 patients with a high- or intermediate-risk of primary myelofibrosis using fedratinib, showed that this drug had a mild impact on serum levels of cytokines but more than half of the patients with myelofibrosis benefited from durable, rapid, and well-tolerated improvements in their clinical manifestations such as fatigue, night sweats, cough, and pruritus [28]. Gandotinib is another JAK2 inhibitor, and clinical trials are ongoing for the treatment of myeloproliferative disorders. The findings of a phase 1/2 trial with 19 subjects indicated a reduction in spleen size in 22% of the patients suffering from myeloproliferative neoplasms. However, the main adverse effects were diarrhea, electrolyte imbalance, anemia, and nausea [29]. A phase 1 study of gandotinib in patients with primary myelofibrosis, polycythemia vera, and essential thrombocythemia showed acceptable safety and tolerability profiles [30]. They suggested that a phase 2 dose of 120 mg was associated with clinical improvement [27]. A phase 2 study of Gandotinib in patients with myeloproliferative neoplasms established an effective response in patients previously treated with ruxolitinib. They reported no significant hematological, neurological, or infectious toxicities [31].

Using a JAKinib to treat a viral infection may play a double role because both type I IFN (IFN- α/β) and type II IFN (IFN- γ) use the JAK-STAT signaling pathway. Cameron et al. [32] conducted a microarray study, which established that patients with SARS who were discharged from hospitals showed low IFN- α and IFN- γ signaling while IFN- α and IFN- γ signaling was evident in patients who died. Nevertheless, the use of pegylated IFN did not lead to beneficial antiviral outcomes and clinical trials with systemic administration of IFN- α/β resulted in conflicting findings. Animal model studies on MERS and SARS diseases demonstrated that IFN- α/β therapy may be beneficial in the early inflammatory phase of both diseases, whereas this therapy is harmful in the late phase of

the diseases [33], suggesting that when hospital care is needed for patients with COVID-19, JAK inhibitors may be a promising approach. Nearly 80% of patients with COVID-19 can eradicate the virus, mostly via antiviral immune responses, especially IFN- α/β . Thus, it is recommended that baricitinib or other JAK inhibitors be given to patients who are admitted to hospitals. Short-term use of baricitinib (i.e., 7–14 days) might reactivate no latent infections, including herpesviruses or tuberculosis, in these patients. Prospective studies (i.e., NCT04320277 and NCT04321993) are ongoing with baricitinib in these patients, which along with appropriate classification, definition of prognostic models, and evaluation of cytokine levels during the early and late phases of the disease, may provide new insights into the treatment of COVID-19 [34].

JAKinib Monotherapy or Combination Therapy with MTX

MTX is a folate antagonist that inhibits the activity of dihydrofolate reductase and the synthesis of purines. It is broadly used for the treatment of RA and psoriatic arthritis, which regresses proliferative cells in the S phase. One of the main MTX mechanisms of action consists of targeting the JAK/STAT pathway [35], thereby downregulating the production of proinflammatory cytokines, i.e., IL-1, IL-12, and TNF- α , while upregulating IL-4 and IL-10 as anti-inflammatory cytokines [36]. However, MTX monotherapy does not significantly affect IL-6 production [37]. Interestingly, Thomas et al. [34] in 2015 reported that MTX could inhibit JAK2 and JAK1 in *Drosophila melanogaster* and several human cell lines, e.g., Hodgkin lymphoma and acute myeloid leukemia, respectively. In silico modeling suggested that this inhibition may be due to direct binding of MTX to the JAK2 kinase domain ATP binding pocket [38]. The combination of MTX with JAK1 or JAK3 inhibitor leads to better clinical outcomes than monotherapy, while its combination with JAK1/JAK2 or JAK1-specific inhibitors does not seem to exert an additive clinical benefit. A phase 3 randomized controlled trial of IL-1 blockade (anakinra) in sepsis demonstrated a prominent survival benefit in hyperinflammatory conditions, without elevated adverse effects [34]. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab (anti-IL-6R) was recently approved in patients with COVID-19 pneumonia and high concentrations of IL-6 in China (ChiCTR2000029765) [39]. Considering mechanisms of

action other than TNF- α inhibition (adalimumab or etanercept), only tocilizumab was established as obviously superior to MTX. Therefore, researchers believe that MTX has an efficacy equal to that of anti-TNF α monotherapy through adenosine and JAK inhibition. These effects possibly explain why MTX monotherapy results in good clinical outcomes resembling those of anti-TNF- α biologics alone but is less effective in comparison to anti-IL6-R alone [40]. MTX plus tofacitinib showed clinical effects similar to those of MTX plus adalimumab [41], suggesting that the specific inhibition of tofacitinib in combination with the JAK1/JAK2 inhibition capability of MTX may exert synergistic effects. There are conflicting data regarding the combination of baricitinib and MTX. A clinical trial reported that MTX plus baricitinib does not result in significantly better clinical outcomes, obtained by baricitinib alone [42]. In contrast, Fleischmann et al. [42] demonstrated that baricitinib monotherapy or combined with MTX had a higher efficacy and safety compared to MTX monotherapy as a treatment for patients with moderate to severe RA [42]. A more recent study showed that baricitinib was approved for either monotherapy or combination therapy with MTX in the treatment of moderate to severe RA [43]. Another study established that structural damage progression was less likely to occur with a combination of baricitinib and MTX rather than MTX or baricitinib alone [44]. Despite all of the possible benefits, JAK inhibition may decrease the host inflammatory response and MTX therapy may predispose the patient to zoster infection as a side effect. All current JAKinibs bind to highly similar catalytic ATP binding sites of JAKs and block them. Nevertheless, these kinds of inhibitors cannot discriminate infected target cells from healthy cells or mutated JAKs from wild-type ones, resulting in potential side effects. Therefore, specific inhibition and no interference with other JAKs remain to be clarified.

Conclusion

ACE2 and AT1-R play pivotal roles in COVID-19 development, and thus targeting of them using novel therapeutic strategies, including recombinant ACE2, ACE inhibitors, ARBs, and Ang 1–7 peptides, may prevent or decrease virus-induced pulmonary, cardiac, and renal damage. However, more studies are needed to clarify the efficacy of these therapeutics. On the other hand, JAKinibs may be beneficial because they may not only reduce the clinical symptoms in the multiple organs such as the

lung, kidneys, and heart (because of blocking AT1-R) that are affected during the disease but also modulate some inflammatory cytokines (because of blocking the actions of type I/II cytokine receptors) that are released during ARDS or cytokine storm conditions. Therefore, JAKinibs are suggested as a promising approach in patients with COVID-19 who are admitted to hospitals. In this regard, it has been recommended that baricitinib or other JAK inhibitors might be given to patients with COVID-19 who are in the late inflammatory phase. Furthermore, there is controversy over combination therapy of baricitinib and MTX or either monotherapy, but according to recent studies the combination of MTX and baricitinib is suggested as a potential approach in the management of COVID-19. The modest safety, cost-effectiveness, and need for a low dose consumption of MTX make it an appealing alternative for combination therapy. Eventually, in addition to antiviral therapy, ACE2 inhibitors, ARBs, and other supportive care, we suggest other potential JAKinibs and novel anti-inflammatory combination therapies that affect JAK-STAT pathway in patients with COVID-19 to improve the treatment process and decrease adverse effects because, although JAKinibs are highly effective, their high cost and adverse effects may limit their application. Therefore, low-cost alternative medications should be introduced to obviate the need for expensive and harmful treatments of COVID-19.

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Availability of Data and Materials

Please contact the corresponding author for data requests.

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Author Contributions

Farhad Seif designed this study and drafted this paper. Hossein Azami was involved in data collection. Majid Pornour and Majid Khoshmirsafa created the figures and interpreted the data. Farhad Seif, Monireh Kamali, and Monireh Mohsenzadegan critically revised this paper for important intellectual content. Davood Mansouri and Majid Pornour supervised this study. All of the authors read and approved the final version of this work.

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