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EXPERT OPINION

Blood Targets of Adjuvant Drugs Against COVID19

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Abstract: While waiting for the vaccine and/or the best treatment for COVID19, several drugs have been identified as potential adjuvant drugs to counteract the viral action. Several drugs, in fact, have been suggested for their ancillary antiviral role. Viral proteases and peptidases, may interact with well-known drugs such as anticoagulants, antihypertensives, antiserotoninergics and immunomodulants. We here report a basic list of these drugs that include bioflavonoids, heparinoids, ACE inhibitors, angiotensin receptor blockers, antiserotoninergics, and monoclonal antibodies against cytokines that may interact with the viral cycle.

Keywords: COVID19, flavonoid, heparin, ace-inhibitors, interleukin, angiotensin receptor blockers

Background

Waiting for the vaccine and/or the best antiviral treatment for COVID19 infection,[1] after its outbreak in the People's Republic of China at the beginning of 2020 and its viral diffusion around the world in the following weeks, several drugs have been suggested for their potential adjuvant support against infection.[2–4]

The pharmacologic actions of these drugs have been suggested after learning about the biological cycle of the RNA coronavirus 19 (ie, n-CoV19). The useful property of these drugs is based on their interference with viral proteases or with viral binding proteins.[5,6]

Drugs that may interact with these viral abilities may exert their actions because of their interference with viral proteases and/or viral ligands.[7,8]

We therefore report the pharmacological properties of several drugs such as flavonoids, heparinoids, ACE-inhibitors, angiotensin receptor blockers, cinanserin and monoclonal antibodies that are able to exert ancillary effects during COVID19 and might possibly be able to improve the outcome of this infection which is associated to increased morbidity and mortality when compared to other recent viral outbreaks. Specific pharmacological activities are summarized in Table 1.

Flavonoids

Flavonoids are an important kind of natural product since they have a polyphenolic structure widely found in fruits and vegetables.[9] They also have antioxidant effects useful in various diseases such as cancer, Alzheimer's disease, and atherosclerosis.[9,10]

Intriguingly, flavonoids also show antiviral activity in vitro. In this way their main action is related to the ability to inhibit viral proteases in particular SARS-CoV 3 C-like protease (ie, 3CLpro).[11]

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Table 1 Reported Drugs Able to Interfere with SARS CoV2

Drug	Main Action	Viral Target
Flavonoids	Antioxidant	SARS 3CL proteases
Cinanserin	Antiserotoninergic	Viral proteases
Heparinoids	Anticoagulant	Viral binding protein
ACE-I	Anti-hypertensives	Viral proteases
Angiotensin receptor blockers	Anti-hypertensives	Viral proteases
Interleukins antagonists	Anti-inflammatory	Viral diffusion
Sacubitril/valsartan	Anti-hypertensives	Viral proteases

Furthermore, flavonoids are also able to interfere with viral binding action with host-cells. This property is related to their affinity with the oligosaccharides of the external cell membrane; in particular, such fucosylated oligosaccharide, present in the extracellular matrix and external cell membrane is the target of the interference between flavonoids and viral action toward the cell membrane. This kind of interaction could also explain a specific selectivity of such coronavirus vs adults and not vs children because of the reduced presence in the extracellular matrix during young age.

Cinanserin

5-HT_{2C} receptor antagonist cinanserin, known for its properties to reduce symptoms of allergy and hypertension, may act also as an inhibitor of proteases. In particular, cinanserin is an inhibitor of the 3C-like protease of SARS-coronavirus and also of other viral proteases as previously reported.[12,13] In particular, cinanserin inhibits coronavirus replicase function using a replicon assay based on HCoV-229E, and inhibits SARS-CoV and HCoV-229E replication in tissue culture.[14]

Additional actions as its immunosuppressive and antiphlogistic properties need to be confirmed by further studies as well as pharmacological actions on neurological functions.

Heparan Sulphate

Heparan sulphate (HS) is an abundant cell-surface Glycosaminoglycan (GAG) that is also present in extracellular matrix and has been widely demonstrated as a binding factor for several viruses;[15] however, other GAGs present on cellular surface as chondroitin sulfate can be similarly identified for their viral binding properties.

From a pathophysiological point of view, HS is abundant in the respiratory tract and so it plays a role as an attachment factor for coronavirus with tropism to bronchitis and other respiratory infections, working in concert with other factors like sialic acid;[16,17] for this reason HS is also able to mediate the attachment of virus to host cells. These actions may explain in part the extended tropism of this virus for cells of respiratory tract.[16,17]

Moreover, HS is also present on the surface of endothelial cells, in particular next to alveolo-capillary areas, and this could be a specific property of SARS CoV2 to induce damage to the lungs.

So, viral actions and viral capacity to bind host cells may slow down in the presence of high doses of HS and this is really important for the pathophysiology of COVID19 infection.[16,17]

Heparins

Unfractioned heparins and low molecular weight heparins have a similar structure to HS so an action similar to HS may be hypothesized during infection of SARS CoV2.

Heparinoids are able to exert their anti-viral activity by increasing the action of several anti-proteases such as antithrombin[18] and other serpin family members.

Moreover, heparinoids interact because of their action toward clotting factors and endothelial cells,[19] and also play a role in the pathophysiology of microvascular thrombosis described in COVID19.[20]

In this field, in fact, as a hypercoagulable state has been testified in several articles in patients with COVID19 infection,[20,21] pulmonary embolism and other types of thromboses may be associated with morbidity and mortality of these patients.

So, heparinoids assume an important role for thromboprophylaxis of venous thromboembolism.[22] Of course, patients with anticoagulant contraindications could not benefit from administration of heparinoids because of the associated risk of major or fatal bleedings.

Ace-Inhibitors

Angiotensin-converting enzyme (ACE), plays the main role for the renin–angiotensin system (RAS), [23] which controls blood pressure by regulation of the volume of fluids into the body. It is a specific peptidase that converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. As other circulating proteases and peptidases, ACE is also

involved in the kinin-kallikrein system that produces bradykinin, a potent vasodilator, that is also able to activate clotting cascade and complement cascade.

The ACE gene encodes two isozymes ACE1 and ACE2.[24] The somatic isozyme ACE1 is expressed in many tissues, mainly in the lung, as well as vascular endothelial cells, as well as epithelial kidney cells, while ACE2 is an enzyme attached to the surface of the cellular membranes of the cells of the respiratory tract. ACE2has been shown to be involved in the entrance of coronavirus into the lung cell and for this reason coronaviruses seem to have a particular avidity for lung cells and are able to induce infections of respiratory tracts.[25]

Based on these data, in experimental models, the infusions of specific drugs such as ACE-inhibitors that are able to block ACE1, have induced a relative availability for ACE2. These data have suggested an increasing susceptibility to develop COVID19 in the presence of SARS CoV2 for patients ongoing therapy with ACE-inhibitors.[25,26]

However, because specific studies in humans in vivo are lacking, although they have planned for the future, a specific recommendation on the daily use of oral ACE-inhibitors in hypertension and in other chronic cardiac diseases for patients with COVID19, is not available.[27,28]

Interestingly, a previous strategy, that added ACE-inhibitors or angiotensin receptor blockers (ARB) to standard therapy for COVID19, has already been reported in the literature in several articles[24,27–30] but with no univocal data.

Therefore, future studies should take into consideration not only the ACE1/ACE2 ratio in users of ACE-inhibitors during COVID19 but also a possible different clinical response in the presence of ACE insertion/deletion polymorphism.

Angiotensin Receptor Blockers

Angiotensin receptor blocker (ARB) are also commonly involved in the treatment of hypertension and other chronic cardiovascular diseases and are able to interfere with RAS system because of their specific binding to angiotensin II receptor.[31] For this reason, they also induce an up-regulation of levels of ACE1 and ACE2 and because ACE2 is one of the proteins involved in the entrance of SARS CoV2 into lung cells, it has been suggested that their use may interfere with the outcome of patients affected by COVID19.[31]

However, as for ACE-inhibitors, specific addressed studies on this outcome are currently lacking in the literature. In the same way the literature did not suggest withdrawal of ARB during COVID19 infection.[32]

Specific addressed studies on this topic have been planned for future years, and also the role of ongoing treatment with sacubitril-valsartan should be under investigation for the frequent presence of heart failure as comorbidity in patients affected by COVID19.[33]

Interleukin Antagonists

Similar to other flu outbreaks, COVID19 also appears to trigger a cytokines' storm in the majority of patients. Based on inflammatory origin, the cytokines' storm involves mainly IL-1, IL-6, IFNγ, and IL-16.[34] For this reason, specific drugs, in particular monoclonal antibodies, have been suggested and tested for the treatment of patients affected by severe clinical form of patients with COVID19.

Patients with COVID19 infection with overt SARS, in fact, show significantly higher levels of IL-6, IL-10, and TNFα. Abnormal levels of circulating cytokines, in fact, are associated to lymphopenia, typically found in COVID19; furthermore, hyper production of cytokines by macrophages (ie, IL-6, IL-2R receptor, IL-10, and TNFα) is associated to hypo-production of IFNγ.[35,36]

Therefore, the role of drugs directed toward IL-6, such as tocilizumab, is justified for increased systemic levels of IL-6 in severe clinical forms of COVID19.[37] Moreover, IL-6 is also crucial to recall virus-specific memory CD4 T cells, [35,36] favoring virus clearance in case of further contacts with SARS CoV2.

Yet, from a clinical point of view, the use of tocilizumab in advanced COVID19 infection suggests that it may improve the outcome of affected patients in particular in a specific subset of patients.[38]

Because of the increase of IL-1 during COVID19 infection, also other monoclonal drugs against IL-1, such as Anankinra have been suggested for the treatment. Randomized trials on this topic have been recently started.[39]

Additionally, IFNγ has been tested as a specific immunological adjuvant drug during other outbreaks mediated by other coronaviruses. Unfortunately, clinical results during SARS and MERS outbreaks did not support its utility in the improvement of related outcomes.[40,41]

Furthermore, some data are emerging concerning the role of vaccination with Bacille Calmett-Guerin (BCG) during SARS CoV2 outbreak. Immuno-adjuvant properties of BCG have been already demonstrated for the treatment of bladder carcinoma.[42]

So, for its immunological properties BCG has been suggested as a possible agent to prevent COVID-19 and

several studies have been planned with this goal.[43] In particular, vaccination has been reported to decrease susceptibility to respiratory tract infections. These data have been taken into account when national data on BGC immunization programs in different countries showed a lower rate of COVID-19 infection in countries in which vaccination is mandatory. Yet, several aspects need to be understood with further specific studies.

Conclusions

We have reported the potential utility of several drugs during COVID19 infection. The interest toward ancillary drugs in this infection was based on data that showed that SARS CoV2is more aggressive than other coronaviruses that induced SARS and MERS outbreaks.

The targets of these drugs are frequently blood circulating proteases and molecules that are also involved in the clotting system or RAS.

In this way, additional actions have been demonstrated by flavonoids and heparins because of their ability to counteract the viral action on the cellular surface and on the extracellular matrix.

Furthermore, cytokines' impairment suggested a specific treatment with anti-cytokines monoclonal antibodies that seem to play a role in more aggressive clinical form of COVID19.

In conclusion, specific studies may be helpful to understand the role of these drugs in the management of COVID19 in order to improve the outcome of affected patients.

Ethical approval and consent to publication

All authors have the agreement of their Institutions to publish clinical experiences in scientific journals.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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