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Combating sars-cov-2 through lipoxins, proteasome, caveolin and nuclear factor-κb pathways in non-pregnant and pregnant populations

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Abstract: It can be misleading to think that the new severe acute respiratory syndrome coronavirus (SARS-CoV2) which has a very strong mutation and adaptation capabilities, uses only the angiotensin-converting enzyme II (ACE2) pathway to reach target cells. Despite all the precautions taken, the pandemic attack continues and the rapid increase in the number of deaths suggest that this virus has entered the cell through different pathways and caused damage through different mechanisms. The main reason why the ACE2 pathway comes to the fore in all scientific studies is that this receptor is located at the entry point of basic mechanisms that provide alveolo-capillary homeostasis. SARS-CoV-2 has to use nuclear factor-κB (NF-kB), caveloae, clathrin, lipoxin, serine protease and proteasome pathways in addition to ACE2 to enter the target cell and initiate damage. For this reason, while new drug development studies are continuing, in order to be beneficial to patients in their acute period, it is imperative that we are able to come up with drugs that activate or inhibit these pathways and are currently in clinical use. It is also critical that we adopt these new pathways to the treatment of pregnant women affected by SARS-CoV-2, based on the scientific data we use to treat the general population.

Key words: SARS-CoV-2; ACE2; Viral entry pathways; Nuclear factor-κB; Proteasome; Lipoxin; Off label drugs; Serine protease.

Introduction

The new severe acute respiratory syndrome coronavirus (SARS-CoV2) is believed to have been transmitted from bats to human via an intermediate host (1). It is an enveloped RNA virus. If SARS-CoV2 reaches adequate colonizationin unciliated alveolar epithelial cells and type II pneumocytescause severe respiratory illness, which is characterized by high fever, cough shortness of breath, and pneumonia (1). Complications such as acute respiratorydistress syndrome, acute renal failure, acute cardiac injury and liver dysfunction may occur if the clinical picture worsens (1,3). Since the new coronavirus, SAR-CoV-2, has a large genetic similarity with other coronaviruses that have previously made pandemics, we may consider that the target cells and entry pathways of SARS-CoV-2 are the same as other SARS-CoV (1). Consistent with this, many studies have reported that SARS-CoV-2 uses angiotensin-converting enzyme II (ACE2) to enter the cell, similar to previous SARS-CoVs (1, 2). ACE2, - a member of the renin-angiotensin pathway, is an aminopeptidase that is attached to the cell membrane and functions as a receptor. Its expression mainly occurs in the type II alveolar cells of the lung, the receptor may express in the placenta, kidney, heart, oral cavity and small intestine (3). However, despite the moderate expression of ACE2 in lung cells, the heavy course of the clinical picture suggests that SARS-CoV-2 also entered the cell through receptors other than ACE2 (Figure 1). Moreover, the glycyl residues in SARS-CoV-2 ensure that the virus binds more strongly to ACE2 than the SARS-CoV (2). This data may explain why the clinical outcome of respiratory failure has worsened despite low ACE2 expression

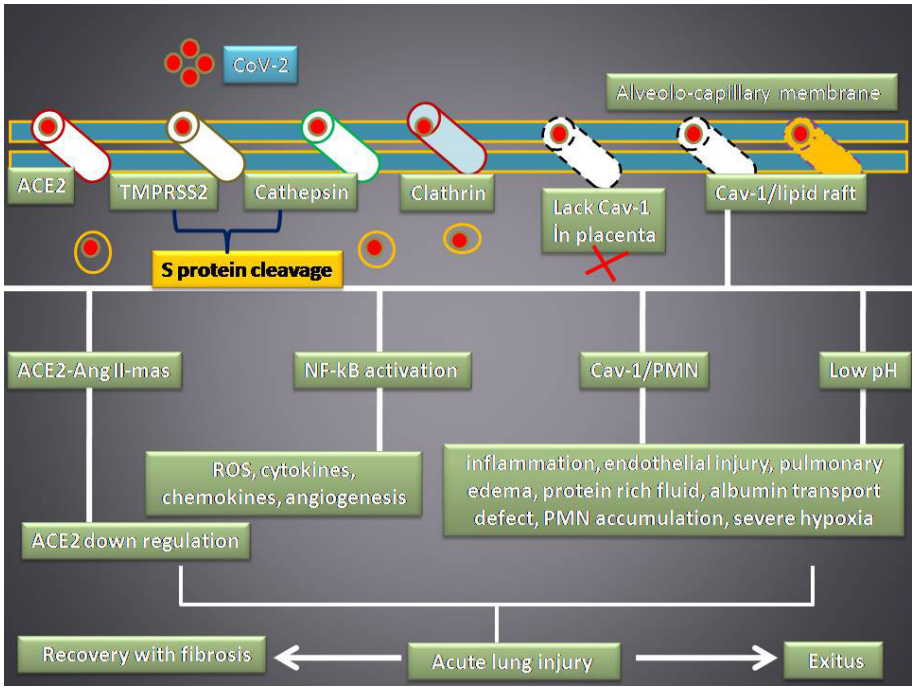

Figure 1. Different entry routes of SARS-CoV-2 into alveolo-capillary membrane. PS: The lack of Cav-1 in placenta that preventing vertical transmission of virus.

in the lungs. Therefore, understanding the viral entry routes is critical in the investigation of new treatment strategies for improving acute lung injury (ALI) caused by new SARS-CoV-2. Unlike normal individuals, so far no precise data on vertical transmission have been found in pregnant women affected by SARS-CoV-2. In this comprehensive review, we will try to explain a new off label treatment agents which, if tested to be effective, would permit a rapid administration in both pregnant and non-pregnant populations with SARS-CoV-2. The most crucial point to consider here is that if we consider using thesenew treatment options we recommend for SARS-CoV-2 in pregnant women, we should definitely consider the teratogenic potential of the drugs and their possible negative effects on the course of pregnancy. It is not unusual to urgently find a new drug to treat SARS-CoV-2. If we can determine all the pathways that the virus uses while entering the cell in detail, we can use the drugs that are in routine use out of indication to inhibit these pathways. Detection of viral transmission pathways comprehensively may also enable the production of new drugs in the post-pandemic period.

Clathrin-mediated endocytosis of SARS-CoV-2

Although some pathways and receptors related to the entry of coronavirus into the cell have been identified, this virus is probably capable of entering the cell through more than one receptor. In addition, depending on the cell type, the entry of the coronaviruses may vary. Clathrin-mediated endocytosis (CME) and cathepsin mediated S protein cleavage is the most important routes for the SARS-CoV and MERS-CoV entry into cells (4). During CME viruses accumulate on the lipid-bilayer membrane before they enter target cells (5). However, coronaviruses utilize a number of alternative pathways such as macropinocytosis, autophagy, caveolar raft endocytosis outside the traditional CME for target cell entry (6,7). Chlorpromazine (CPZ) is an inhibitor for clathrin-dependent endocytosis and blocks the entry of SARS-CoV and MERS-CoV into cells (8,9). The use of CPZ in the treatment of SARS-CoV-2 is not reported yet.

Reasons that make pregnancy susceptible to viral infections

It is clearly shown that the clinical outcome of SARS-CoV-2 in pregnant women is milder than those in SARS-CoV and MERS-CoV (10). However, we think it is early to make definitive comments on this issue. The number of pregnant cases is not enough to make a real scientific comment about the disease outcome that is being caused by SARS-CoV-2. Unlike alveolar entry, the transmission mechanism of the SARS-CoV-2 between the mother and the fetus differs due to the physiological features of the placental cells. The unique structure of the placenta requires a careful scientific approach in the suggestions to be made regarding the intrauterine transmission of SARS-CoV-2. Generally, compared to the non-pregnant population pregnant women and their fetuses represent a high-risk group during infectious disease outbreaks. The death of approximately two-thirds of the pregnant women who had SARS-CoV or MERS-CoV pandemics revealed how susceptible the pregnant women to infections affecting the lungs (11). We can explain the possible reasons for this as follows. (i) In addition to the immune system changes physiological and mechanical changes during pregnancy (12), the lungs become more sensitive to the destructive effects of the viruses. (ii) The dominance of the T-helper 2 (Th2) pathway against T-helper 1 (Th1) with advancing pregnancy is another physiological process that leaves pregnant women vulnerable to viral infections (13). Combating viruses mostly belong to the Th1 pathway. The Th2 pathway has a function that protects the fetus mostly. Even these physiological changes are sufficient to follow up on the pregnant women infec-

ted with SARS-CoV very closely.

Contrary to the views mentioned above, some authors argue that physiological changes related to pregnancy are protective against viral infections. Hormonal changes during pregnancy and Th2 dominance can create an anti-inflammatory effect, making the clinical course related to SARS-CoV-2 milder than non-pregnant patients (14). Moreover, the physiological increase in progesterone synthesis during pregnancy may neutralize the inflammation in lung cells due to viruses by blocking the nuclear factor-κB (NF-κB) pathway, the cellular marker of inflammation. In addition, about 0.3°C increase in body temperature due to progesterone increase may limit the proliferation of coronaviruses, which are negatively affected by the temperature. Although the presence of genetically reduced ACE2 expression in women is not very clear, it can protect pregnant women against SARS-CoV-2 (15). Due to the lack of sufficient caveolin expression in the trophoblastic cells forming the placental barrier, all cells in the barrier can be protected from virus-related cell damageand vertical transmission (16).

Caveolae; the main initiator of acute lung injury

Caveolae are deposits that resemble the omega marking located on the plasma membrane. They are available as free cytoplasmic vesicles within cells (17). Caveolae consist of caveolin-1 protein (Cav-1) and are responsible for the rapid transport of extracellular substances to intracellular organelles such as the endoplasmic reticulum or golgi (18). Cav-1 also interacts closely with cell wall cholesterol and lipids (19). High cholesterol and sphingolipids contents of caveolae make them be classified as a lipid raft (20). They are involved in the internalization of some viruses. Both alveolar and endothelial cells of the lungs express Cav-1 isoforms (21). Reducing cholesterol levels in the circulation or plasma membrane leads to flattening of caveolae (22). This data brought up the idea that drugs that inhibit cholesterol synthesis can prevent the entry of viruses to the alveolar cells. On the other hand, viral entry occurs via a caveolae-independent endocytic pathway in patients with SARS-CoV (23).

Although SARS-CoV-2 does not need the caveolae to enter the target cellsit does not exclude the possible role of caveolae in the emergence of acute lung injury (ALI). The presence of more than one caveolin binding sites on coronavirus is an important data supporting the possible relationship between ALI and SARS-CoV-2 (24). Although members of the coronavirus family do not use the cav-1/caveolae pathway to enter the lung cells they trigger the cav-1 system and lead to ALI formation (25). The initial phase of ALI is evident by activation of NF-κB, destruction of the alveolar-endothelial membrane, accumulation of protein-containing fluid, the release of reactive oxygen species (ROS) and cytokines, collection of polymorphonuclear leukocytes (PMNLs),subsequently interstitial fibrosis and severe hypoxia. During the early phase of ALI, PMNLs initiate the activation of the intracellular pathway (25,26). By activating PMNLs Cav-1 begins inflammation, endothelial injury, and alveolar edema relatedtoALI (27). In the lungs of most patients recovering from ALI, stiffness is detected due to increased fibrosis. Antiproliferative and proapoptotic features of cav-1may lead to an antifibrotic effect on lung fibroblasts. This finding suggests the possibility that the ALI developed due to SARS-CoV-2 may occur with a caveolae-mediated mechanism. SARS-CoV-2 does not use caveola for cell entry, but by binding to the caveola, activates post-receptor mechanisms to initiate PMNL-mediated lung injury. Therefore, the use of cholesterol synthesis inhibitors can alleviate lung damage, although they do not prevent viral entry.

Endosomal pH neutralization with lysosomotropic substances

Whether pH is alkaline or acidic is not critical to a successful attachment of viruses to the cell membrane. However, decreased pH values are required for the active use of endocytotic pathways by the virus (28). By diffusing into acidic endosomes lysosomotropic substances may neutralize the endosomal pH, leading to the prevention of virus replication. An acidic pH in endosomes is required for SARS-CoV-2 to enter the target cells easily (29). Chloroquine phosphate (CQ) is an anti-malarial drug and has lysosomotropic, antiviral and immunomodulating activities. Accordingly, CQ has been reported to reduce viral infection when used in adequate doses in SARS-CoV infection (30). CQ also impairs cell attachment by disrupting the glycosylation of SARS-CoV-2 receptors (29). Following administration, CQ accumulates in the endosomes and lysosomes subsequently neutralize the endosome-lysosomal acidic pH. Drop-in endo-lysosomal pH inhibits the protease functionand thus prevents cell fusion and viral entry (29,31). For this reason, CQ therapy can reduce viral proliferation and surface protein synthesis by lowering intracellular pH. This makes us think that CQ treatment has an antiviral effect through a pH-dependent mechanism (32). These data allow us to use other options such as alkaline fluid consumption or alkaline nutrition, which will change the intracellular pH in alkali direction, for prophylactic purposes in viral pandemics (32).

In order for SARS-CoV to attach to the ACE2 receptor and enter the cell, it is necessary to cleave the S protein through proteases. This is a pH dependent process (32). Hence, neutralization of intracellular pH by CQ treatment breaks the protease functions and inhibits the S protein priming thusblocks the viral entry. Wang et al reported that ACE2 receptors exposed to CQ were trapped within perinuclear vacuoles suggesting that CQ may inhibit the ACE2 receptor (23). Since ACE2 serves as the receptor for SARS-CoV-2 and CQ prevents the SARS-CoV-2- ACE2 attachment this anti-malarial drug can be used for prophylactic purposes in SARS-CoV-2 pandemic.The use of CQ in pregnant and non-pregnant patients affected by SARS-CoV-2 provided the clinical and serological improvement (33). Hence, many countries have stocked this drug in case of a possible increase in the number of patients requiring hospitalization. In addition to the studies reporting it's a beneficial effect there are also studies indicating that it has no positive contribution to the course of the disease. In an article published during the revision of this article, it was reported that the use of CQ alone or in combination with azitromycin did not reduce mechanical ventilation rates

or even increase total mortality (34). The reason for the difference between studies may vary depending on the time of CQ initiation or in which group of patients it is used. Both CQ and its metabolites pass through the placenta. However, since there is no data indicating that it has negative effects on the fetus, CQ can be used by considering other side effects in pregnant women affected by SARS-CoV-2 (33).

ACE2 and TMPRSS2: Basic cell entry routes of SARS-COV-2

The type II transmembrane serine protease 2 (TMPRSS2) is the basic protease on the plasma membrane of alveolar cells (35). TMPRSS2 promotes replication and syncytium formation of coronavirus in vitro and in vivo (36). TMPRSS2 also provides basic protease activity for SARS-CoV-2 replication (37). Spike protein of SARS-CoV-2 uses the ACE2 as the main receptor binding site (38). However, ACE2 interaction with SARS-CoV-2 spike protein requires serine protease activation. This interaction is essential in viral passage to lung cells. During SARS-CoV-2-ACE2 engagement SARS-CoV-2 employs theTMPRSS2for its spike protein primingthat is essential for SARS-CoV-2entry (39). Nevertheless-blocking this receptor reduces the infection but does not eliminate itentirely (37). It has been shown that the clinically proven protease inhibitor camostat mesylate prevents the entry of SARS-CoV-2 into target cells by inhibiting TMPRSS2, but not completely canceled (37). This data suggests the presence of other receptors that continue the entry of SARS-CoV-2 into the lung cell by maintaining the S protein cleavage other than TMPRSS2. Furin-mediated S protein cleavage may be a possible mechanism for maintaining viral entry. Likewise, spike protein cleavage of SARS-CoV-2 can be simplified by cathepsin L, trypsin or elastase (36). The role of these two pathways should be explored in detail and urgently. Lopinavir/ritonavir, which are viral protease inhibitors, have been used and found useful in patients affected by SARS-COV-2 infection (40). However, there is no sufficient data on the use of both camostat and other viral protease inhibitors in pregnancy.

If SARS-CoV-2 is capable of entering any type of cell expressing ACE2, there is a risk of vertical transmission in the fetuses. Although extensive ACE2 expression throughout the placenta has been reported the presence of ACE2 alone is not sufficient for passage through the placenta (41). SARS-CoV-2 must cleave S protein via TMPRSS2 before adhering to ACE2. Since we do not have any clear scientific data on whether the presence of TMPRSS2 in placental cells, we cannot make a definitive comment about the vertical transmission of the virus.

Low TMPRSS2 expression in trophoblast cells during early placentation may restrict the vertical transmission of SARS-CoV-2. The risk of vertical transmission may increase following 24th gestational weeks because of the TMPRSS2 expression increases in the maternal-fetal interface (42). However, clinical studies have failed to clearly report whether the presence of vertical transmission in patients with SARS-CoV-2 (43).

The ACE2-Ang-Mas axis should remain functional by using ART1 blockers or recombinant human ACE2

ACE2 is a member of the renin-angiotensin familyand has two different forms as full length and soluble. The full-length ACE2 contains a transmembrane domain, which puts over its extracellular domain to the cell membrane. The soluble form does not contain the membrane anchor and circulates in small amounts in the blood (44). While ACE turns AngI into AngII, ACE2 removes a residue from AngI to obtain Ang1–9. ACE2 also removes a single residue from AngII to get Ang1–7 (45,46). Lung cells contain ACE2-Ang-(1-7)-Mas receptor complex and the expression of this complexis positively associated with the severity of ALI (47). By binding its receptor ACE2 shows a potent antagonistic effect against ACE in the lungs (45). Accordingly, it has been reported thatthe ACE2-Ang-Mas receptorcomplex has a preventive effect on the emergence of ALI (48). While in the pneumocytes ACE, AngII and Ang II receptor type 1 (AT1R) induce lung-injury, ACE2 and AngII receptor type 2 (AT2R) protect from lung cells from an acute injury (45).

Using AT1R blockers increases the expression of ACE2 protein in hypertensive patients (49). In the light of this data, we can think that the increase in ACE2 due to AT1R blockers may cause worsening of the clinical course by allowing more viruses to enter the cell because ACE2 is the main binding site of SARS-CoV-2. However, in clinical practice, vice versa develops and SARS-CoV-2 infected patients treated with AT1R blockers show less lung injury (50). Despite all these positive effects, the data is not sufficient to suggest the use of AT1R blockers as a therapeutic agent in the SARS-CoV-2 infected patients (51). However, the fact that patients who have been using AT1R blockers for a long time due to hypertensive disorders are infected with SARS-CoV-2 is not an indication for stopping this drug. Data on the use of AT1R blockers in pregnancy is unclear. Although they are not major teratogens, the use of AT1R blockers in pregnancy is not recommended. Accordingly, exposure to AT1R blockers is related totoa increased fetal risk than exposure to ACE inhibitors. The risk of fetopathy is significantly increased in those exposed to the drug after the 20 weeks of gestation (52). Unlike this work, a study by Hoeltzenbein et al. reported that there was no clear proof for an increased risk for spontaneous abortions or preterm birth in hypertensive pregnant women using AT1R blockers in the first twelve weeks of pregnancy (53).

If we use human recombinant ACE2 (rACE2) and AT1R inhibitors together, it will be possible to alleviate the ALI developing due to SARS-CoV-2. Using rACE2 is an approach with pros and cons. We can use rACE2 for the purpose ofcompetitive interceptor (54). Hence we can think that rACE2 may reduce the amount of virus that reaches lung cells by capturing circulating SARS-CoV-2. However, keeping the ACE2 pathway functional via application of rACE2 will lead to the continuation of entry of SARS-CoV-2 into target cells. It may seem like a handicap that the virus continues to enter the cell, albeit a little. However, this negative effect will alleviate the ALI by ensuring that the ACE2-Ang-Mas receptor complex remains functional. In this

context, it is obvious that there is a need for a treatment that will activate the ACE2-Ang-Mas axis without using rACE2. The first thing that comes to our mind here is the lipoxins which are capable of keeping this receptor complex functional during ALI. The potentially beneficial effect of rACE2 to alleviate SARS-CoV-2 should be urgently tested.

Lipoxins attenuates SARS-CoV-2-induced lung injury via ACE2-Ang-Mas axis

Lipoxins (LXs) are generated from arachidonic acid through the lipoxygenase enzyme in the presence of molecular oxygen (55). LXs work by binding to ALX/FPR2, a G-protein-coupled receptor (56,57). Lipoxin A4 (LXA4) and aspirin-triggered Lipoxin A4 exhibit an important role in the inhibition of inflammation and promote inflammation resolution in ALI (58). LXA4 inhibits the inflammatory response (59) by decreasing the synthesis of ROS (60) and controlling the NF-kB pathway (61). Recovery of lung inflammation is an active process and is controlled by a special group of lipid mediators (62,63). During ALI, LXA4, epi-LXA4, and resolvin are produced at the district of inflammation and prevent the PMN passage into lung cells and facilitate resolving the inflammation (62-64). A recent study showed that aspirin-triggered 15-epi-LXA4 can improve failed phagocytosis and bacterial clearance and restore PMN-dependent pulmonary inflammation (57). Another study by Chen et al (61) showed that the application of LXA4 preventedthe pneumocytes from LPS-mediated ALI through the ACE2-Ang-Mas axis. While the LXA4 administration was also increased the expression of inflammatory cytokines decreased the levels of inflammatory cytokines and ROS. LXA4 also inhibited the LPS induced NF-κB activation in alveolar cells (65). If we can inhibit the cyclooxygenase enzyme with specific inhibitory drugs and the lipoxygenase pathway remains functional, circulating LX levels increase in ALI patients due to SARS-CoV-2. Increased LXs levels can reduce the amount of ROS and NF-κB, allowing the ALI to recover quickly. Since LXs realize their anti-inflammatory and antioxidant effects via the ACE2-Ang-Mas axis this receptor complex should be kept active continuously. To keep the ACE2-Ang-Mas axis active, either AT1R blockers should be used or recombinant ACE applications should be done. The close relationship between the LXs and the NF-κB pathway will also help us find new forms of drugs necessary to keep this axis active (Figure 2).

NF-κB: a promising pathway for off label drug discovery

The protective roles of ACE2-Ang-Masaxis in ALI due to SARS-CoV have been reported to occur through anti-inflammatory and anti-oxidation mechanisms (45, 48, 65). It has also been reported that the presence of functionally active ACE2-Ang-Mas axis inhibits the PMNLs accumulation, decreases the generation of ROS, and preventsthe activation of NF-κB (66). As well as ROS and cytokines the activation of the NF-κB pathway plays an important role in the formation of acute lung injury (67). The initiation of inflammatory events in the alveolo-capillary membrane is maintained by the ROS, open reading frame (ORF) of viruses and cytokine-induced by NF-κB pathway. Orf9c interacts with many proteins that regulate the NF-κB pathway (68). Hence, there may be a close relationship between Orf3b, Orf10 of SARS-CoV-2 and NF-κB pathway (69). NF-κB is the main transcription factor that provides activation of genes responsible for immune and inflammatory events (70).Activation of related genes leads to worsening of inflammation, inducing neoangiogenesis, and inhibiting apoptosis (71). Moreover, NF-κB activation initiates the inflammatory process called the cytokine storm, leading to the uncontrolled release of IL-1b, IL-6, IL-12, and TNF-alpha (72). This process leads to rapidly developing lung injury followed by acute respiratory distress syndrome that requires respiratory support. Because of

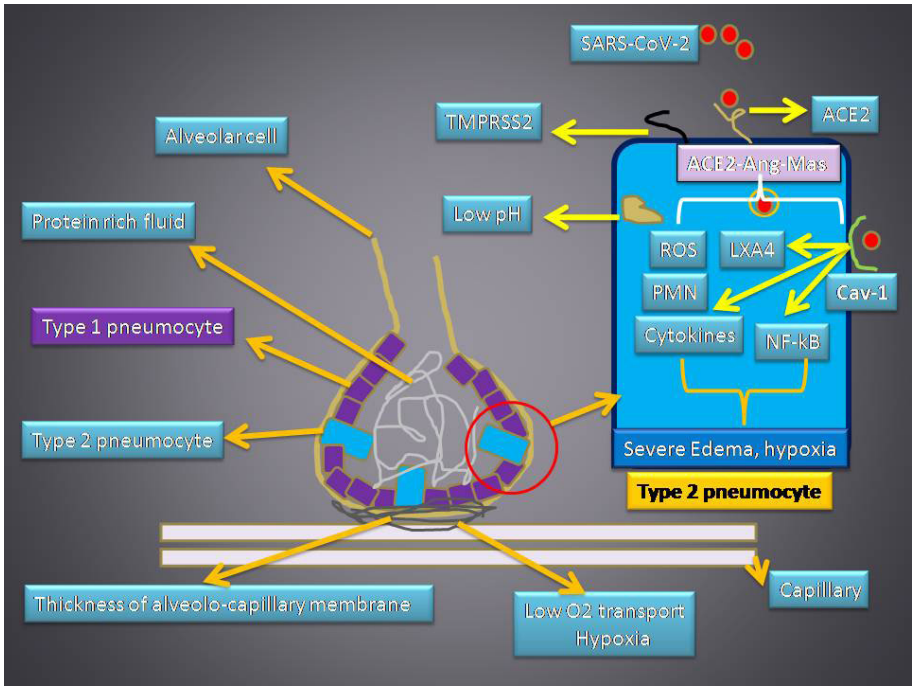

Figure 2. Mechanism of acute lung injury mediated by SARS-CoV-2.

these reasons, inhibition of the NF-κB pathway is of great importance in the treatment of lung damage due to SARS-CoV-2 infection.It is possible to block the NF-κB pathway by using either specific NF-κB inhibitors or proteasome inhibitors (70,73). By regulating intracellular protein breakdown proteasomes improve cell hemostasis and prevent inflammation (74). Bortezomibis a well-known proteasome inhibitor (74).Its main function is the inhibition of the NF-κB pathway (75). Since Bortezomib is an important drug of myeloma therapy with manageable side effects we can use it in well-chosen cases with SAR-CoV-2 (76). However, data on the use of this drug in pregnancy are limited.

Progestins are physiological NF-κB inhibitors with fewerside effects. Likewise, danazol reduces interleukin production by inhibiting the NF-κB pathway (77). Sulindac, a nonsteroidal anti-inflammatory drug,inhibitsthe DNA binding of NF-κB.We can consider using these three NF-κB blockers in non-pregnant patients affected by SAR-CoV-2. However, the cytotoxic and immunosuppressive effects of danazol restrict its use in pregnant women (78). Likewise, the use of NF-κB blockers in pregnant patients affected by SARS-CoV-2 should be decided considering the profit and loss rates. To summarize briefly the neutralization of endosomal acidic pH with CQ, inhibition of the cav-1 pathway with statins and inhibition of the NF-κB pathway with progestins, danazol, sulindac or bortezomib can further alleviate the ALI outcome. Increasing the production of aspirin-triggered LXA4 can be used to rapidly regress ALI by blocking both NF-κB and ROS systems (Figure 2).

Antiparasitic drugs Pak1 Pathway and SARS-CoV-2

Ivermectin can be therapeutic in SARS-CoV-2 by blocking IMPα/β1-mediated virus transport. However, ivermectin also activates autophagy, which is not preferred for viral infection treatment. Actually, the exact role of autophagy in mediating viral entry of SARS-CoV-2 remains debatable (3,4). PAK1, a serine/threonine-protein kinase, plays an important role in spike protein cleavage and attachment of the virus to the ACE2 receptor (79). Hence, PAK1 may be a potential therapeutic target for SARS-CoV-2. Similar to tumor cell autophagy, by promoting PAK1 degradation via the proteasome-dependent mechanism ivermectin could induce SARS-CoV-2 autophagy (80). Ivermectin inducedautophagy may, therefore, increase the entry of the virus into the target cell. Together, this drug does not appear to be suitable for use in SARS-CoV-2 cases. The effect of this drug, which is in clinical use and has low side effects, in nonpregnant and pregnant populations affected by SARS-CoV-2 should be tested immediately.

Can we use neutralizing antibodies directed against the viral S protein of patients recovering from previous SARS-CoV outbreaks in SARS-CoV-2 cases?

If there is a 76% amino acid sequence similarity between SARS-CoV and SARS-CoV-2 S proteins, we can use antibodies from the serum of convalescent patients affected by SARS-CoVs in the treatment of SARS-CoV-2 cases. A new study on this subject reported that neutralizing antibodies from convalescent SARS-S- patients reduced SARS-S-2-mediated cell entry. However, the decrease in the SARS-CoV-2 entry was significantly less than that in the SARS-CoV entry (37). For this reason, we find it useful to say that the use of such neutralizing antibodies is somewhat effective. Instead, it may be more appropriate to use S protein antibodies in patients who have recovered from SARS-CoV-2 disease. Since SARS-CoV-2 employs TMPRSS2 for priming its spike protein the inhibitors of TMPRSS2 receptor and convalescent serum of SARS-CoV cases can be used together. Since the TMPRSS2 inhibitor camostat mesylate is currently approved forclinical use in chronic pancreatitis it can be used for this purpose. In this way, the impact of neutralizing antibodiescan be potentiated. This prediction is a pandemic emergency that requires further investigation.

Other off label drugs or supplements

In addition to the pathways mentioned above and the drugs acting on these pathways, many drugs or supplements are recommended as an adjunct to the treatment of SARS-CoV-2 in the light of not well-designed studies or past experiences. We find it useful to briefly touch on these recommended drugs.

High dose Vitamin C: No clear contribution of high dose C Vitamine administration alone or in combination with other drugs to disease progression has been demonstrated (81).

iNO: Inhaled nitric oxide (iNO) is a drug used for the treatment of children with acute hypoxemia due to persistent pulmonary hypertension (82). There is no study on the use of this drug in SARS-CoV-2, but we think it is worth trying

Tocilizumab/sarilumab: It has been reported that the use of these drugs, which are IL-6 antagonists, during the cytokine storm, reduces fever and the need for oxygen (83).

Interferon-beta-1a: It can be used to suppress viral replication that develops due to corticosteroid use. There are subcutaneous and inhaled forms (84).

Dornase alfa: Dornase alfa is a recombinant DNase used in the treatment of cystic fibrosis. It cleaves the DNA released from the PMNs and reduces mucous viscosity and prevents intravascular thrombosis. Unfortunately, neutrophil extracellular traps (NET), a degradation product resulting from PMN degradation, increases the inflammatory events and protease activity, leading to the expansion of tissue damage. For these reasons, its use as an off-label drug in SARS-CoV-2 treatment may worsen existing lung damage (85,86).

Mesenchymal stem cell (MSC) or stromal vascular-fraction (SVF), pluristem'allogenic placental expanded cell (PLX): Different forms of stem cell therapy can be useful in the treatment of SARS-CoV-2 by reducing inflammation or regulating the release of immunomodulators. However, there are insufficient data on the use of these treatments in the treatment of coronavirus patients, except for small case series. The easy availability of PLX and SVF can allow them to be used in the near future treatment of patients with SARS-CoV-2 (87,88). It should be remembered that routine off-label prescribing these drugs should be avoided until there is data to support a drug's use in SARS-CoV-2. Thus, it is

ensured that patients who really need these drugs can access them easily.

Conclusions and notes to take home

Our suggestions to treat SARS-CoV- before the transmission or early disease period can be summarized as follows;

- The recommended rules should be followed carefully to prevent transmission of the virus.
- Intracellular pH should be neutralized. For this purpose, lysosomotropic agents such as Chloroquine can be preferred. Alkaline fluid consumption or alkaline nutrition can also help this purpose.
- The use of Chlorpromazine should be tested for inhibition of clathrin-dependent endocytosis.
- It should be considered to prevent PMN-mediated lung injury by blocking the caveolar/lipid raft pathway with statins.
- TMPRSS2 pathway should be blocked by using serine protease inhibitors and spike protein priming should be prevented.
- The use of ART1 blocker or soluble recombinant human ACE2 should be further developed.
- The use of AT1R blockers does not worsen the clinical picture.
- ACE2-Ang-Mas receptor complex should be kept functional through lipoxins.
- Aspirin-triggered Lipoxin A4 is critical in resolving inflammation.
- NF-κB and proteasome pathways should be blocked with specific inhibitors. For this purpose, bortezomib, danazol, sulindac and progestins should be included in the treatment agenda.
- It should be urgently tested whether progestins, a natural NF-κB inhibitor, are responsible for resistance to SARS-CoV-2 in women and pregnant women.
- If convalescent patient sera are used together with the TMPRSS2 receptor inhibitor, camostat, the effect of neutralizing antibodies may be potentialized.
- Since Ivermectin stimulates PKA-1-mediated autophagy, it can increase the entry of the virus into the cell.
- The effects of high-dose vitamin C and Dornase alfa use on the clinical course of the disease are not clear.
- Although the mucolytic effect of Dornase alfa is an advantage, it can provoke NET-mediated cell damage.
- Since they can positively affect the course of the disease the need for well-designed clinical trials on the use of SVF and PLX in therapy is evident. Efforts should be made to use all the above-mentioned drugs in pregnant women, considering the side effects and teratogenicity potentials.
- Weak expression of cav-1 in placental barrier cells appears to be the primary mechanism preventing vertical transmission. For this reason, cav-1 pathway should be taken into consideration for the development of new drugs.

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