Mast Cell Stabilizers as a Supportive Therapy Can Contribute to Alleviate Fatal Inflammatory Responses and Severity of Pulmonary Complications in COVID-19 Infection

Destekleyici Bir Tedavi Olarak Mast Hücre Stabilizatörleri COVID-19 Enfeksiyonunda Ölümcül İnflamatuar Yanıtları ve Pulmoner Komplikasyonların Şiddetini Hafifletmeye Katkıda Bulunabilir

Abstract
SARS-CoV-2 (COVID-19) leads to severe acute respiratory syndrome by settling the pulmonary system. Mast cells (MCs) are multifunctional immune cells that are extensively distributed throughout the body and mostly present in pulmonary system. MCs play a vital role in acquired and innate immunity, and to maintain immune homeostasis of the body through a wide range of mediators in their cytoplasmic granules. Severe respiratory syndrome with proinflammatory cytokine release and pneumonia during COVID-19 infection can result in the death, in particular in debilitated individuals or those suffering from related chronic disorders. In this review, we attempt to discuss potential relationship between COVID-19 symptoms and mast cells as well as potential use of mast cell stabilizers as a supportive therapeutic option in COVID-19 infection.

MCs are main source of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α as well as bronchoconstrictor mediators such as histamine, prostaglandin-D2 and leukotriene-C4 that can lead to fatal inflammatory responses and pulmonary complications during COVID-19 infection. SARS-CoV-2 may activate MCs through toll-like receptors or by inducing the cross-linking of the IgE-FcεRI, thus leading to release of those mediators. SARS-CoV-2-induced abnormal production and release of these mediators from MCs can further exacerbate inflammation in respiratory system, consequently pulmonary complications.

Therefore administration of MC stabilizers as a supportive therapy may be useful to alleviate inflammatory responses and pulmonary complications in order to reduce deaths from SARS-CoV-2 infection.

Keywords: SARS-CoV-2; COVID-19; mast cells; inflammatory mediators; mast cell stabilizers.

Öz
SARS-CoV-2 (COVID-19) pulmoner sisteme yerleşerek ciddi akut solunum yetmezliği sendromuna yol açmaktadır. Mast hücreleri vücudta yaygın dağılım gösteren ve pulmoner sisteme bol miktarda bulunan çok fonksiyonlu bağışıklık hücreleridir. Mast hücreleri doğal ve kazanılmış bağımsızca ve vücudun bağımsızlık homeostazının sürdürülmesinde sitoplazmik granüllerindeki çeşitli mediyatörler aracılığıyla hayati bir rol oynamaktadır. COVID-19 enfeksiyonu sırasında pro-inflamatuar sitokin salınımı ve pnömoni ile karakterize ağır akut solunum yetmezliği özellikle zayıf veya ilişkili kronik hastalıklardan muzdarip bireylerde olümle sonuçlanabilme teşebbüsü. Bu derlemede COVID-19 semptomları ve mast hücreleri arasındaki potansiyel ilişkisini ve destekleyici bir terapötik seçeneği olarak mast hücre stabilizatörlerinin COVID-19 enfeksiyonunda potansiyel kullanımını tartıştık.

Mast hücreleri, COVID-19 enfeksiyonu sırasında olümülü inflamatuar yanıtları ve pulmoner komplikasyonlar tetikleyebilen IL-1, IL-6 ve TNF-α gibi pro-inflamatuar sitokinlerin ve histaminin, DOI: 10.21673/anadoluklin.720116

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Background

Outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or novel coronavirus (2019-nCoV) continues to cause the deaths worldwide (1). As of April 12, 2020, a total of 1,696,588 confirmed cases and 105,952 deaths have been announced by the World Health Organization (2). Coronaviruses are enveloped RNA viruses and widely permeated among humans, other mammals, and birds (3). Coronaviruses lead to respiratory, enteric, hepatic, and neurologic diseases (4). SARS-CoV-2 belongs to the genus Coronaviruses. COVID-19, which is now rapidly spreading and becoming a pandemic, has been first identified and isolated from patients with pneumonia in Wuhan, China (3). It causes principally a severe acute respiratory disease.

Transmission

It is considered that the virus was first transmitted most probably from animal to human on the Huanan seafood market in Wuhan, China. Notwithstanding COVID-19 is speculated to be originated from bats, its certain resource, animal reservoir and enzootic patterns of transmission are not yet accurately known (5). However, increases in the number of cases worldwide demonstrate frankly that COVID-19 is also transmitted from human to human. It is known that transmission of the virus from human to human occurs principally through respiratory tract, by droplets, respiratory secretions, and direct contact with an infected person who has the viral symptoms including cough and sneezing (6). When anybody inhales air borne droplets from infected person, the virus arrive at the respiratory tracts and the lungs. But until now, it has not been reported that whether a person who touched the infected surfaces or objects will be infected by COVID-19. However, after the transmission, the virus enters ciliated epithelium in the respiratory system. Although not yet certain, it is postulated that the virus may probably enter to cells in the ciliated epithelium by using angiotensin converting enzyme 2 (4). Then the virus is replicated in such cells and leads to cellular damage and infection at infection site.

Diagnostic criteria

It has been reported that until now the securest clinical diagnosis method for COVID-19 is to detect nucleic acid (RNA) of the virus in the swab samples of nose and throat, or the other respiratory tract samples such as bronchoalvelor lavage fluid by real-time polymerase chain reaction (6).

Clinical symptoms

It has been reported that most common symptoms of COVID-19 infection include fever, cough, fatigue, sputum production, dyspnoea, sore throat, haemoptysis, diarrhoea, lymphopenia as well as headache (4, 6). Fever and cough from those common symptoms are mostly seen, on the contrary upper respiratory symptoms and gastrointestinal symptoms are reported as scarce (6, 7). In addition to pneumonia, acute respiratory distress syndrome, septic shock, metabolic acidosis and even the death can occur specially in elderly individuals and patients who have one of such disorders such as hypertension, chronic obstructive pulmonary disease, diabetes, cardiovascular disease (6, 8).

Treatment

Currently almost all of the world suffers from COVID-19 outbreak and pneumonia caused by it, and the number of COVID-19 positive cases and deaths are rapidly increasing day by day worldwide. Unfortunately, a special vaccine for COVID-19 has not yet been developed although the scientists have worked...
hard to achieve this. However, the physicians have administered only supportive therapies such as use of antipyretic agents, maintenance of hydration, mechanical ventilation for respiratory support and use of antibiotic in bacterial infections to ameliorate the clinical symptoms (4). Therefore supportive therapies are of vital importance to struggle against life-threatening symptoms of COVID-19 such as pneumonia, severe acute respiratory distress syndrome, septic shock and metabolic acidosis.

**Mast cells**

Mast cells (MCs) are multifunctional immune cells originating from CD34+/CD117+ myeloid progenitor cells in the bone marrow (9). MCs are extensively distributed throughout the body and present in mucosal and connective tissues. MCs participate in a great variety of physiological and pathophysiological conditions such as innate and adaptive immunity, inflammation, allergies, asthma, eczema, interstitial cystitis, irritable bowel syndrome, migraine and pulmonary hypertension (10-13). When activated, MCs release a wide range of the pre-formed and de novo synthesized mediators mediating those physiological and pathophysiological situations through their degranulation (14, 15). MCs store a large number of vasoactive and pro-inflammatory mediators, proteases, cytokines, chemokines, and growth factors such as substance P (SP), serotonin, prostaglandins, bradykinin, histamine, tumor necrosis factor-α (TNF-α) interleukin (IL)-1β, granulocyte-macrophage colony stimulating factor etc in their cytoplasmic granules (16-18). MCs can be activated by immunologic and non-immunologic stimuli such as IgE, antigens, anaphylatoxins, viruses, bacteria, toxins, detergents, food additives/preservatives, xenoestrogens, neuropeptides, cold, exercise, radiation and pollutants (19, 20). While mild activation of MCs under physiological conditions is needed to maintain homeostasis of body systems, their overactivation causes immunological disorders mentioned above. Therefore, stabilization of MCs are of vital importance to treat MC activation-related disorders and to ameliorate symptoms caused by immunological reactions. Life-threatening immunological processes following pathological stimuli such as COVID-19 can be restrained using endogenous and exogenous mast cell stabilizing agents.

**Mast cell activators and mechanisms of mast cell activation**

MCs can be activated in immunoglobulin E (IgE)-dependent and IgE-independent manners. Mature B-cells generate IgE antibodies in response to CD4+ Th2 cells (21). MCs express FcεRI receptors on the cell surface. IgE is mostly present bound to the high-affinity receptors, FcεRI, on MCs (9, 22). When an antigen entering the body through virus or the other sources comes into contact with MCs, MCs are activated by cross-linking of the IgE-FcεRI, and release contents of the granules to their resident environments (9, 22). IgE is present in the respiratory tract, connective tissue under epithelial layers of the skin, as well as in the gastrointestinal tract (21). Additionally, MCs express different receptors including Fc receptors, toll-like receptors (TLR), as well as receptors for chemokines, cytokines, and pathogen-associated molecular patterns which are related to MC activation and immune responses (21, 22). Particularly TLR is expressed both on the cell membrane and in the cytosol of MCs and able to recognize viruses, bacteria and fungi.

Moreover, some hormones and neuropeptides including corticotropin-releasing hormone, substance P, calcitonin gene-related peptide and neurotensin are capable of stimulating the activation of MCs through G-protein coupled receptors in the cell membrane of MCs (23,24). In addition, it was reported that pituitary adenylate cyclase activating peptide-38 evoked rat peritoneal and dural MCs degranulation through the phospholipase-C pathway (25). Cytokines including stem cell factor (SCF), IL-3, IL-4, IL-9, IL-33 are able to activate MCs (23). Histamine from MCs can cause degranulation of human MCs via H4R receptor (26). It was stated that several chemokines such as CXCL12 and CCL11 can selectively stimulate mediator release from MCs (27). In addition to the above, there are also more endogenous MC triggers such as insulin-like growth factor-1, stem cell factor, leptin, acetylcholine, estrogen, β-endorphin, nitric oxide etc. (28).
Mast cell stabilizers

Mediators from MCs are involved in a wide range of conditions such as itching, allergies, conjunctivitis, asthma, mastocytosis, pain, and neurodegenerative disorders. Therefore, MC stabilizers are of vital importance in the prophylaxis and treatment of mast cell activation-mediated disorders. MC stabilizers can be categorized primarily as endogenous and exogenous mast cell stabilizing agents.

**Endogenous stabilizers of mast cells**

MCs perform their physiological functions in the body by balancing between degranulation and stabilization conditions. By balancing degranulation/stabilization of MCs, endogenous stabilizers of MCs play a vital role in controlling activation of MCs and consequently in the immune homeostasis of the body. It was demonstrated that heparin and chondroitin sulphate from MCs are able to inhibit the activation of MCs (29). Spermine in MC granules was shown to prevent MC secretion in rats (30). Moreover, progesterone and testosterone from sex hormones show inhibitory effects on the MC activation (31, 32). It was reported that beta receptor agonists blocked MC activation by inhibiting release of mediators such as histamine, TNF-α and prostaglandin D2 (33, 34). Additionally, there are different endogenous molecules which are able to inhibit degranulation of MCs such as corticosterone, cortisol (28), anandamide, 2-arachidonoyl glycerol (2-AG) (35, 36).

**Exogenous stabilizers of mast cells**

In addition to endogenous stabilizers of MCs, there are also present various exogenous stabilizers of MCs including synthetic (e.g. ketotifen), semi-synthetic (e.g. indanone and pterosin Z), and plant-derived mast cell stabilizers (e.g. cromolyn, quercetin and luteolin). Cromolyn sodium is prominent drug of such MC stabilizers. It is used in treating MC-related disorders such as asthma.

SARS-CoV-2 may activate mast cells in the respiratory system through toll-like receptors or by inducing the cross-linking of the IgE-FcεRI. Activated mast cells release pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α as well as bronchoconstrictor mediators such as histamine, prostaglandin-D2 and leukotriene-C4. Abnormal production and release of these mediators from mast cells can further exacerbate SARS-CoV-2-induced inflammation in the respiratory system. Therefore endogenous or exogenous stabilizers of mast cells may alleviate inflammatory responses and pulmonary complications by suppressing activation of mast cells in SARS-CoV-2 infection. TLR: toll-like receptor, TNF-α: tumor necrosis factor-α, IL: interleukin, LTC4: leukotriene-C4, PGD2: prostaglandin-D2.
Allergic rhinitis, allergic conjunctivitis, and mastocytosis (37). In addition, ketotifen is another mast cell stabilizer however it has also antagonistic effect for histamine-1 receptor (38). Spleen tyrosine kinase (Syk) inhibitors like compound-13, R-112 and ER-27317 are synthetic inhibitors of MCs that are able to inhibit the signal transduction of the allergic reactions such as asthma, anaphylaxis and allergic rhinitis (39). Another chemical group of MC stabilizers is JAK3 inhibitors that prevent activation of MCs by inhibiting JAK3 signaling pathway (40). Additionally, kit tyrosine kinase inhibitors are also an important group of chemical stabilizers of MCs (38). It was shown that hypothemycin blocked FcεRI-mediated activation of MCs and also cytokine production from MCs by inhibiting Kit kinase activity (41). Moreover, inhibitors of phosphodies-terases are considered to be chemical stabilizers of MCs due to the fact that they inhibit the activation of MCs (42). Recently, there is an emerging interest to plant-derived mast cell stabilizers, quercetin and luteolin. Because it was demonstrated that quercetin and luteolin have potent inhibitor effect against human mast cells. Apart from these, we have previously showed that a synthetic peptide salmon calcitonin suppressed glyceryltrinitrate (a nitric oxide donor)-induced activation of meningeal MCs (18). In addition to this, we have recently demonstrated that phytochemical agent thymoquinone inhibited the degranulation of meningeal MCs induced by glyceryltrinitrate (43).

**Potential relationship between COVID-19 symptoms and mast cells, and the importance of mast cell stabilizers**

Up till now, there is no yet a special vaccine or effective drug for COVID-19. Therefore supportive therapies are needed to reduce the life-threatening symptoms and consequently deaths. Prominent symptoms of COVID-19 including severe lung failure, dyspnoea, pneumonia, septic shock, and the ground-glass opacities are held responsible for most of the deaths from the infection (44).

As mentioned above, MCs contain a wide variety of vasoactive and highly inflammatory mediators, such as histamine, IL-1, IL6, TNF-α, interferon-γ (IFN-γ) and IL8(CXCL8) (16). When activated, MCs release those mediators by explosive extrusion of mediator-containing granules, which characterizes anaphylactic degranulation, or by release of granular contents a process called piecemeal degranulation (45).

TLRs expressed by MCs are able to recognise viruses, bacteria and fungi. SARS-CoV-2 may activate MCs through TLRs or by inducing the cross-linking of the IgE-FcεRI, thus leading to release of those inflammatory mediators. SARS-CoV-2-induced abnormal production and release of these mediators from MCs can further exacerbate inflammation in respiratory system.

In any case, proinflammatory cytokines such as IL-1, IL6 and TNF-α and IL-8 are chief mediators of inflammation and fever in conditions induced by viruses, bacteria and fungi. It is clear that these mediators released as a result of activation of MCs can exacerbate inflammation in lungs during SARS-CoV-2 infection. Viral infections can evoke IL-1 release, which, in turn leads to lung and tissue inflammation, fever and fibrosis (46, 47). It was suggested that IL-37 can inhibit inflammation in SARS-CoV-2-induced inflammatory state by suppressing IL-1β, IL6 and TNF due to the fact that these mediators are involved in lung inflammation, fever and fibrosis (46, 48-51).

Previously in a clinical study was demonstrated that plasma levels of IL-1beta were markedly increased while plasma levels of IL-6 and TNF-α were mildly raised in pediatric patients with SARS-associated coronavirus infection (52). In another study, authors showed the elevated expressions of IL-1β, IL-6 and TNF-α in the SARS-CoV-infected ACE2+cells in lung and bronchial autopsy tissues from four patients who died of SARS (53). Oka-bayashi and colleagues demonstrated that SARS-CoV evoked elevated levels of IL-6 in SARS-CoV-infected Caco2 cells compared with other respiratory viruses including influenza A virus and human (54). Moreover they also showed that SARS-CoV infection evoked upregulation of TLR 4 and 9 which are associated with the initiation of inflammatory response (54). Additionally, it was stated to be a potent relationship between IL-6 peak levels and...
severity of pulmonary complications in COVID-19 infection (51).

As mentioned above, when it is considered that MCs express TLRs, we can speculate that SARS-CoV-2 may lead to activation of MCs in pulmonary system which, in turn, induce immune responses. Moreover cytokines released from activated MCs such as IL-1, IL6 and TNF-α and IL-8 would in turn further exacerbate the inflammation state. In this state, although use of IL-1, IL-6 and TNF-α blockers seems as plausible to alleviate severity of inflammation, and consequently pulmonary complications in COVID-19 infection, this may lead to weaken total immune response of the body. Moreover, it was reported that anti-TNF-α agents are contraindicated in SARS-CoV-2-infected subjects (51). Instead of these, use of MC stabilizing agents as a supportive therapy may be useful to alleviate inflammatory responses in order to reduce mortality.

In addition, a lot of mast cell-derived mediators such as histamine, prostaglandin (PG)D2 and leukotriene (LT)C4 have been known directly to affect airway smooth muscle function. In particular, these three mediators including histamine, PGD2 and LTC4 evoke bronchoconstriction, mucus secretion and mucosal oedema, thus making difficult breath process (46, 47, 55). It is well known that histamine leads to the bronchoconstriction via H1 receptors in the respiratory system, in particular in asthma condition. Additionally, it was suggested that tryptase from MCs can also lead to bronchoconstriction in experimental studies (55). During SARS-CoV-2 infection, these potent constrictor mediators from activated MCs can endanger the life of the patients through potent bronchoconstriction of airways. Administration of endogenous or exogenous mast cell stabilizing agents during COVID-19 infection may preserve the patients against bronchoconstriction mediated damages, and also promote to fight the infection.

Pulmonary fibrosis is a condition with progressive fibrosis in lungs that may cause pulmonary dysfunction and decreased quality of life in SARS survivors after recovery. It has been suggested that pulmonary fibrosis may be one of the main complications in patients with COVID-19 infection (47, 48, 56). It has not been yet stated the mechanisms underlying COVID-19-induced pulmonary fibrosis, but based on the existing theoretical basis, we can speculate that mediators from SARS-CoV-2-activated pulmonary MCs may contribute to this condition. Our reasoning is in line with the literature reporting MC mediators led to pulmonary fibrosis. Those studies reported that mediators from activated MCs are able to enhance migration and proliferation of fibroblasts in vitro (57), and MCs also enhance the fibrosis in a number of organs (58, 59). It has been proposed that the number of connective tissue mast cells is raised in inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (60, 61). In addition, it was stated to be an increase in chymase expression which is a connective tissue MC-derived mediator in human idiopathic interstitial pneumonia (62). Moreover, it was shown that connective tissue mast cells were increased in fibrotic areas of the alveolar parenchyma in patients with idiopathic pulmonary fibrosis (63). In a recent paper has been suggested that IL-1 induced by viral infections is also involved in pulmonary fibrosis (47). Therefore, in the context of these reports, it may be reasonable inhibition of pulmonary MCs by endogenous or chemical stabilizers of MCs in preventing pulmonary fibrosis in COVID-19 patients.

Taken together, severe pneumonia induced by human coronaviruses including SARS-CoV-2 is closely connected with rised pro-inflammatory cytokine responses resulting in acute pulmonary injury and severe acute respiratory syndrome. Mast cells are main source of pro-inflammatory cytokines and bronchoconstrictor mediators that can lead to fatal inflammatory responses and pulmonary complications during COVID-19 infection. Therefore administration of MC stabilizers may be of prime importance among existing supportive therapies. A hypothetical illustration for potential mechanisms of SARS-CoV-2-induced mast cell activation and alleviation of the symptoms by mast cell stabilizers is shown in figure 1.

Someone might argue that the immune system of the body may weaken in combating COVID-19 infection when activation of MCs are suppressed by
MC stabilizers. However, we speculate that i) mild stabilization of MCs by MC stabilizers may be useful, ii) the other immune cells continue to produce related mediators in order to combat the infection due to immune cells of the body are not only MCs but also the other defense cells such as white blood cells, tissue macrophages, T and B cells, iii) respiratory system contains substantial amounts of MCs in the body.

In conclusion, we suggest that MC stabilizers as a supportive therapy may be a promising candidate in attenuating fatal inflammatory responses and respiratory distress in order to reduce deaths in COVID-19 infection.

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