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The therapeutic potential of regulatory T cells in reducing cardiovascular complications in patients with severe COVID-19

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ABSTRACT

The SARS coronavirus 2 (SARS CoV-2) causes Coronavirus Disease (COVID-19), is an emerging viral infection. SARS CoV-2 infects target cells by attaching to Angiotensin-Converting Enzyme (ACE2). SARS CoV-2 could cause cardiac damage in patients with severe COVID-19, as ACE2 is expressed in cardiac cells, including cardiomyocytes, pericytes, and fibroblasts, and coronavirus could directly infect these cells. Cardiovascular disorders are the most frequent comorbidity found in COVID-19 patients. Immune cells such as monocytes, macrophages, and T cells may produce inflammatory cytokines and chemokines that contribute to COVID-19 pathogenesis if their functions are uncontrolled. This causes a cytokine storm in COVID-19 patients, which has been associated with cardiac damage. Tregs are a subset of immune cells that regulate immune and inflammatory responses. Tregs suppress inflammation and improve cardiovascular function through a variety of mechanisms. This is an exciting research area to explore the cellular, molecular, and immunological mechanisms related to reducing risks of cardiovascular complications in severe COVID-19. This review evaluated whether Tregs can affect COVID-19-related cardiovascular complications, as well as the mechanisms through which Tregs act.

1. Introduction

The SARS coronavirus 2 (SARS CoV-2) infects target cells by attaching to the angiotensin-converting enzyme-2 (ACE2). Coronavirus disease (COVID-19) is caused by the SARS coronavirus 2 (SARS CoV-2) [1]. This viral disease, which has a mortality rate of 2.2%, causes various symptoms such as nausea, cough, acute respiratory distress syndrome (ARDS), severe pneumonia, cardiovascular complications, and organ dysfunction [1,2].

COVID-19 has so far appeared in four waves [3]. The latest one has been caused by the new Omicron variant [4]. Previous waves were related to the Ancestral, Beta, and Delta variants [4]. In comparison to previous variants, the Omicron variant had a lower rate of hospital admissions and a lower severity of COVID-19 [5,6]. The mortality rate of Omicron variant has been reduced significantly from the original 2.2 [7,8]. The high levels of previous infection and vaccination coverage are likely responsible for the changing clinical presentation of SARS-CoV-2 Omicron infection [9]. However, due to ability of COVID-19 to produce

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repeat infection, a critical concern has been whether humans will experience reinfections with this pathogen, which might enable COVID-19 to become endemic [10].

Tregs, which comprise 5–15% of the $CD4^+$ T cells in the peripheral blood [11], play a significant role in maintaining self-tolerance and suppressing autoimmunity [11–14]. Tregs express several cell surface molecules, including CD25, CD45RA, CD45RO, CD62L, CD127, CD103, cytotoxic T-lymphocyte antigen-4 (CTLA-4, or CD152), CCR6, HLA-DR, CD39, CD95, ICOS, CD147, glucocorticoid-induced TNF receptor family-related gene (GITR), and programmed cell death 1 (PD-1) that enable them to be isolated and characterized [15]. Furthermore, FOXP3 is a Treg-specific transcription factor that plays a significant role in Treg differentiation, development, and function [16]. In addition, IL-2 as a T-cell growth factor has contributed to developing and promoting natural Treg activity [17].

Tregs are divided into two major groups: those originating from the thymus (nTregs) and those induced in the periphery (iTregs). Immature $CD4^+$ T cells with a high self-antigen affinity differentiate into natural Tregs during the T cell growth process (nTreg) in the thymus [18]. nTregs are recognized by the expression of CD4, CD25, and FOXP3 markers [18].

Inducible Tregs (iTregs) are Tregs derived from virgin CD4+ T cells in the presence of TGF-β in the peripheral tissues that respond to exogenous or self-antigens [19–21]. iTregs and nTregs are different regarding their epigenetic status and stability [22]. In addition, iTregs are characterized by their cytokine profile [19]. In humans, a variety of iTreg subsets have been recognized, including $CD8^+$ Treg, Th3, Tr1, and natural killer Treg (NK Treg) [22]. These iTreg subsets suppressed immune responses, while they differ in cell surface markers and formation sites [22].

Through direct cell interaction and the release of anti-inflammatory cytokines, both natural and iTregs regulated the proliferation and activities of innate immune cells (dendritic cells and macrophages). They also suppressed self-reactive lymphocytes, including Th1, Th2, Th17, and B cells [23]. IL-10 and TGF-β are multifunctional cytokines secreted by different immune cells, including Tregs (primarily Th1 and Th3) and Th2 cells [24]. IL-10 producing nTregs contributes to eliminating pathogens in viral, fungal and, bacterial infections [25,26]. TGF-β has been implicated in maintaining natural Tregs in the thymus and inducing iTregs differentiation [27]. TGF-β was found to play a role in Th17 cells differentiation [28–30]. Tregs release IL-35, which inhibits T-cell proliferation by binding to the IL-12R2 receptor [31].

Aside from nTregs FOXP3-positive T cells could be polarized from FOXP3-negative T cells in the presence of TGF-β [32]. It was also shown that activation of Tregs producing high amounts of TGF-β with the addition of IL-6 induces $CD4^+CD25^+Foxp3^-$ T cells to differentiate into IL-17-producing cells in the absence of other cells [33]. Hence, activated Tregs themselves differentiate into IL-17-producing cells in the presence of a source of IL-6. However, cytokines may enhance the proliferative response and potentiate their FOXP3 expression and suppressive activities. One of these cytokines is interferon β (IFNβ) used for multiple sclerosis therapy [34,35]. One of the mechanisms of cytokine actions is induction of the proliferation of $CD4^+CD25^+Foxp3^-$ regulatory T cells through up-regulation of GITRL on dendritic cells [35]. From the view of this point, $CD4^+CD25^+Foxp3^-$ T cells have dual effects on the course of an immune response that includes the immune status in COVID-19 infection [32,33].

Recent research suggests that Tregs phenotype and function may be unstable in an inflammatory environment, with unanticipated plasticity toward Th1 and Th17 cells in autoimmune diseases and viral infections [20,36]. Tregs may lose their regulatory function and even show a pro-inflammatory activity [20]. Explanations for Treg plasticity include epigenetic and posttranslational modifications [36]. It was found that Tregs converted into Th1-like cells producing IFN-γ, co-expressing FOXP3 and Tbet (the main transcription factor of Th1 cells) with the upregulation of CXCR3 other classical Th1 markers *in vivo* [20]. The presence of IFN-γ producing cells was also observed in FOXP3 expressing cells after PMA/Ionomycin stimulation or after prolonged *in vitro* expansion of $FOXP3^+$ Tregs [20]. Th1-like Tregs are associated with several autoimmune diseases in humans, including T1D (type-1 diabetes) and multiple sclerosis (MS) [20]. Additionally, it was demonstrated that Treg-Th17 conversion occurred in the presence of IL-1β and on epigenetic modifications resulting in the up-regulation of ROR-γ (the specific transcription factor of Th17 cells) expression [20,37,38]. Th17-like conversion *in vivo* was recently proposed for tumor-infiltrating Tregs isolated from human ovarian tumors [39]. Interestingly, according to the findings, Tregs produced in the presence of vitamin C + RA established a more stable population when exposed to an inflammatory environment *in vitro* or *in vivo* [36], suggesting a possible strategy for reducing Treg plasticity in inflammatory conditions like in COVID-19 infection.

According to our knowledge, very little research has been done to investigate or hypothesize the effects of Tregs on cardiovascular complications in severe COVID-19 infection. Therefore, this review aimed to seek whether the cardiovascular complications caused by COVID-19 infection could be affected by Tregs as well as the mechanisms by which Tregs act.

2. COVID-19

COVID-19 is a respiratory viral infection generated by the SARS coronavirus (SARS CoV-2), first found in Wuhan, China, in December 2019 [40]. The World Health Organization (WHO) announced the new coronavirus is a worldwide outbreak on March 11, 2020 [41].

SARS CoV-2 is a coronaviridae virus with a single-stranded RNA genome [42]. This virus has a genome that is about 30,000 nucleotides (27–32 kb) and encodes structural and accessory proteins [42]. SARS-CoV preserves 79% and 50% of its genetic sequence with MERS and SARS-CoV-1, two other coronaviridae viruses, respectively, and attaches to ACE2 as the receptor for cell infection [43]. According to a large body of evidence, COVID-19 infection causes multi-organ dysfunction in the lung, heart, brain, large intestine, kidneys, and spleen compared to other coronaviruses that are only concerned with respiratory infections express the ACE2 receptor [43–48].

In the normal viral clearance process, COVID-19 recruits and activates T-helper 1 cells (Th1 CD4+ cells) at the site of inflammation, which can eliminate infected cells and prevent the virus from spreading and replicating [48]. Neutralizing antibodies could then block viral attachments to cells, and macrophages would then phagocytize the neutralized viruses as well as apoptotic cells [48]. The viral load rises during the first week of infection and gradually decreases over the next few days. SARS CoV-2 antibodies start to rise 10 days after infection, and most patients become seroconverted within the first twenty days [49].

3. Immunopathology of COVID-19

It has been shown that alternations in the proportions of immune cells have been associated with progression, severity, and death in most severe COVID-19 patients [50–53]. The total neutrophils are increased while total lymphocytes are reduced, increasing the neutrophil-lymphocyte ratio (NLR) in these patients [50,51]. Patients with severe COVID-19 also tend to have a lower frequency of basophils, monocytes, and eosinophils [54]. Moreover, increased neutrophils and decreased lymphocytes have been shown to correlate with the severity of COVID-19 infection [55].

Lymphopenia in COVID-19 patients has been found in several studies [56–60]. In severe COVID-19 patients, lymphocytes were less than 5% within two weeks of disease onset [56–60]. Despite the decrease in T cell numbers, their functions were normal [61] or even hyper-activated, as evidenced by the high proportion of HLA-DR (a marker of TCD4+ cell activation) and CD38 (a marker of TCD8+ cell activation) double-positive populations [62,63].

It was found that B and T lymphocytes and NK cells were significantly diminished in severe COVID-19 patients [64–66]. However, T-cell frequency (both T $CD4^+$ and $TCD8^+$ cells) are more impaired than other immune cells [61], SARS-CoV-2 affects the proportion of T helper $CD4^+$ subpopulations including, Th1, Th17, Th2 cells, and Tregs, in COVID-19 patients in a different manner [67,68].

During COVID-19 infection, both anti-inflammatory (Th2) and pro-inflammatory (Th1) responses are activated, resulting in an increase in several cytokines (IFN-γ, IL-6, IL-1, TNF-α, IL-12, IL-10, and IL-2) in severe COVID-19 infection [67,69]. SARS CoV and MERS CoV usually caused Th1 immunity, contributing to excess secretion of inflammatory cytokines (IFN-γ, IL-12, TNF-α, and IL-1), related to significant pulmonary complications a high death rate [70,71].

In patients experiencing severe COVID-19, the percentage of Tregs decreased dramatically while the percentage of Th17 cells (as the inflammatory cells) increased [61,72], resulting in a decline in the Treg/Th17 cell ratio [62,73]. The reduced Treg/Th17 ratio is associated with the unregulated systemic inflammation in acute lung damage, like acute respiratory distress syndrome [74,75]. Reduced Treg numbers in severe COVID-19 cases reflect inadequate modulation of pro-inflammatory immune reactions, which could exacerbate inflammatory reactions and tissue damage [76].

Inflammation has already been identified as the main contributor to the pathogenesis of severe COVID-19 [77]. Excess pro-inflammatory cytokine production has been shown in COVID-19 cases due to elevated Th17 cell activity [62,68]. IL-17A and CXCLs chemokines attract myeloid cells like neutrophils to the infection site and activate matrix metalloproteinase. This leads to the recruitment of more inflammatory cells like Th1 and Th17 cells and the excessive secretion of inflammatory cytokines, which intensifies uncontrolled systemic inflammation [68]. This is known as a "cytokine storm," resulting in tissue damage and viral sepsis, both of which have fatal consequences [68]. Other symptoms of severe COVID-19 include acute respiratory distress syndrome and respiratory and cardiac failure [68].

Indeed, augmented levels of circulating TNF-α, IL-6, and IL-1 (the major pro-inflammatory cytokines) cause naive $CD4^+$ T cells to differentiate into Th17 cells while inhibiting Tregs, resulting in a Treg/Th17 ratio imbalance [22]. Inducing tissue factor expression on mononuclear cells could lead to coagulation activation and thrombin production, resulting in disseminated intravascular coagulation (DIC) and, eventually, pulmonary embolism [22]. In addition, it may have a role in the rapid decline in pulmonary oxygen exchange shown in COVID-19 patients [22]. TNF-α and IL-6 levels in the blood have been proposed as determinants of disease severity [22].

4. Cardiac damage in COVID-19

Cardiovascular diseases are the most frequent comorbidity detected in COVID-19 patients [78–80]. The mortality risk in COVID-19 patients with cardiovascular diseases is more significant than in COVID-19 patients with other disorders such as diabetes mellitus and chronic pulmonary disease [74,75]. In COVID-19 patients, increased levels of several cardiac injury biomarkers were found, including cardiac sensitivity troponin I (hs-TnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) [12,15]. COVID-19-induced heart inflammation resulted in various clinical outcomes, including right ventricle and cardiac amyloidosis, concentric left ventricular hypertrophy with a dilated left ventricle, and severe hypokinetic arrhythmias (ranging from tachycardia and bradycardia to asystole) [12].

SARS CoV-2 can affect cardiac tissue either directly or indirectly [22] (Fig. 1). The expression of ACE2 by cardiac cells such as pericytes, cardiomyocytes, vascular smooth muscle cells, and fibroblasts could enable SARS CoV-2 to infect these cells directly [22,81]. Inflammatory cytokines and chemokines including IL-2, IL-6, TNF-α, IL-1, monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 1- (MIP-1), which are the main contributors of cytokine storm, are implicated in the cardiac injury indirectly. [11,13,14,16,18,19,22,82–85]. This indicates that the immune system plays a part in cardiovascular complications in COVID-19 patients as infiltration of monocytes and T cells observed in autopsies

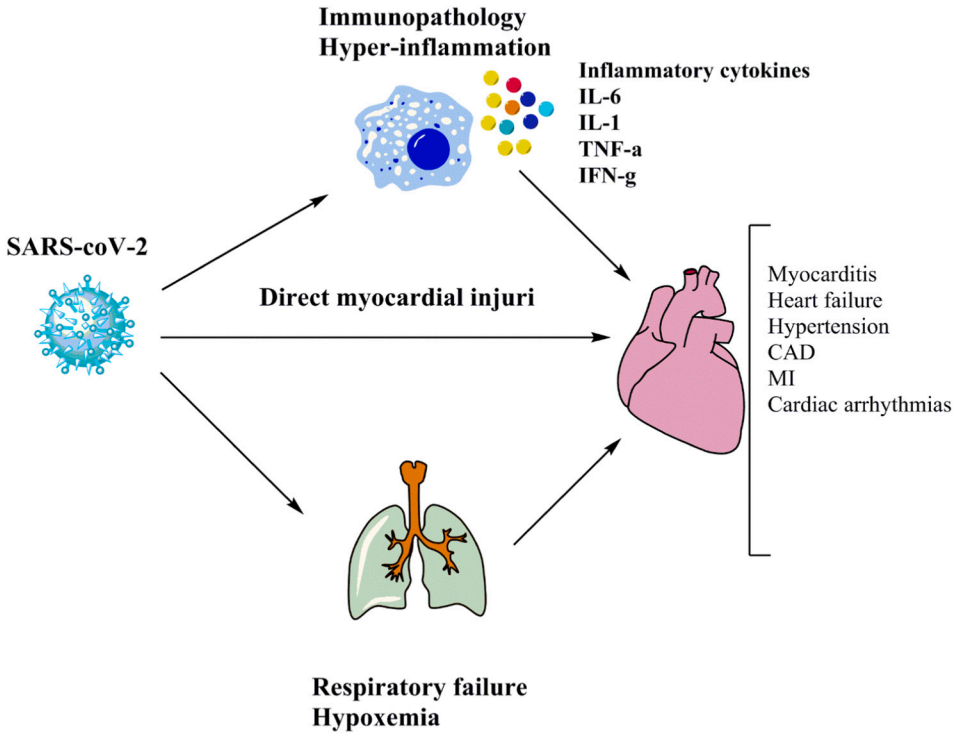


Fig. 1. Proposed mechanisms of cardiac injury.
Cardiac tissue may be influenced by SARSCov2 infection (or Covid19) directly or indirectly. ACE2 expression by cardiac cells could directly infect these cells by a coronavirus. Indirectly, inflammatory cytokines that are the leading cause of cytokine storms are implicated in cardiac damage.

[11,13,14,16,18,19,22,62,82–86]. Mononuclear infiltrates are associated with areas of cardiomyocyte necrosis, which determines myocarditis in COVID-19 patients according to the Dallas criteria [87,88]. Elevated levels of inflammatory cytokines and chemokines may lead to myocarditis, heart failure, hypertension, coronary arterial diseases (CAD), myocardial infarction (MI), and cardiac arrhythmias [24–26]. In addition, hypoxemia, metabolic disturbances, systemic inflammation, or myocarditis may all cause arrhythmias in patients whit COVID-19 [89–91]. These patients can experience acute coronary syndromes due to the elevated thrombotic proclivity, as shown by increased D-dimer levels, although the incidence of such cases is unclear [89–91]. Heart failure is another risk associated with coagulation defects in COVID-19 patients [27].

5. Tregs impairment in COVID-19

According to current evidence, the frequency of peripheral Tregs is significantly reduced in patients with severe COVID-19 infection compared to patients with moderate disease [61,72,92]. It is important to note that Treg depletion in mice infected with murine coronavirus resulted in a rise in acute encephalitis mortality, demonstrating the protective role of Tregs during acute COVID-19 infection [93]. Obesity is also a risk factor for COVID-19. Evidence from obese subjects and relevant animal models showed that the percentage of Tregs in the blood and visceral adipose tissues is low, indicating a higher state of inflammation in obese individuals [94].

The following are possible explanations for the reduction of Tregs in severe COVID-19:

IL-2 serves as a growth factor for Tregs by increasing the expression of FOXP3 (the master transcription factor of Tregs) [95]. As observed in the bronchoalveolar lavage of patients with severe COVID-19, decreased IL-2 levels may lead to Tregs apoptosis and decreased FOXP3 gene expression [95]. Furthermore, inflammatory conditions in severe COVID-19 patients probably improve proteolytic cleavage of cell surface CD25 (IL-2R), resulting in increased levels of soluble CD25 [61,72]. Soluble CD25 may potentially interact with IL-2 signaling and bioavailability, contributing to rising Treg apoptosis (Fig. 1) [61,72].

One of the reasons for the decrease in the percentage of Tregs in peripheral blood is the possibility of Tregs migrating to the lungs to regulate adverse inflammatory responses in patients with COVID-19 [96]. As noted, Tregs can suppress inflammation [23], leading to the regulation of the activity of macrophage, Th1, and Th17 cells that are contributed to cytokine storm occurrence during viral infection [23]. As previously mentioned (Section 3), the cause of cytokine storm could be due to uncontrolled inflammation and inappropriate immune responses leading to severe lung damage which is the leading cause of morbidity and mortality in COVID-19 [97]. In this light, it has been proposed that Treg therapy may be one option for treating patients with severe COVID-19 [97,98]. However, the dosage of Tregs and complementary therapies for SARS-CoV-2 infection must be approached [98]. A study demonstrated that three transfusions of allogeneic cord blood Tregs substantially reduced the levels of the major cytokines that contributed to the cytokine storm, including IL-12, IL-6, TNF-α and, IFN-γ [98]. In addition, after transfusion of Tregs, the levels of IL-8 and MC-1 (two well-known chemokines in lung injury) also drastically were diminished [98].

6. The role of Tregs in cardiac homeostasis and various cardiovascular complications

Tregs are contributed to cardiac, immune tolerance, and the breakdown of immune tolerance to self-antigens in the heart may cause cardiac inflammation [99]. According to recent research, Tregs are essential for vascular and cardiovascular function [100]. PDL-1 expression in the heart cells as a ligand of PD-1 (one of the functional surface markers of Tregs) may support that point [99]. Tregs in the heart have higher proliferative rates than Tregs in blood and lymphoid tissue, suggesting that local renewal is particularly important for Tregs expansion in the heart, even in the absence of cardiac injury [101]. In addition, tolerogenic DCs were detected in the heart tissue that primed antigen for Treg cell activation [102]. The development of an inflammatory network, which involves inflammatory cell aggregation and the production of inflammatory cytokines, can affect the progression of cardiovascular diseases [103]. As a result, suppressing inflammatory responses is a potential candidate for preventing and treating myocardial infarction, atherosclerosis, myocarditis, heart failure, and hypertension [103]. Clinical trials indicated that the frequency and function of circulating Tregs were lower in patients with chronic heart disease relative to healthy individuals [104,105]. Tregs can suppress the pro-inflammatory cells and the production of pro-inflammatory cytokines, both of which are associated with cardiovascular complications [103]. Tregs dysfunction may lead to uncontrolled inflammatory responses of Th1 and Th17 cells and, consequently, myocardial infarction and heart failure [106].

Myocarditis is an inflammatory cardiac disease caused by various infectious agents and autoimmune diseases [107–109]. Viral infections could trigger myocarditis by inducing immediate cytotoxic reactions, post-viral inappropriate immune responses, and autoimmunity [103]. Tregs protected against myocarditis in animal models infected with Coxsackievirus B3 (CVB3), hepatitis C, and herpes simplex virus by minimizing viral-induced immunopathology and suppressing tissue injury due to viral-induced immunological responses [110].

Infiltration of different inflammatory cells including, neutrophils, monocytes, and lymphocytes (particularly Th1 and Th17 cells) in the myocardium, increased the severity of myocarditis [103]. Tregs have been reported to regulate inflammatory cells activation, which limits the anti-viral immune response and prevents myocarditis progression [103,111]. It was discovered that adoptive transfer of Tregs reduced viral load and immune cell infiltration in the heart, in the pancreas and, in the spleen, which was associated to decrease expression of the coxsackie-adenovirus receptor (CAR), less activation of p38 MAP kinase, and increased Akt activation [112,113]. These alternations were caused by TGF-β, which triggered a paracrine positive feedback loop and converted naive $CD4^+$ T cells into regulatory $CD4^+$ T cells [111]. So, inhibition of p38 MAP kinase is an effective strategy in treating viral diseases [114]. The P38 Mitogen-Activated Protein (MAP) Kinase is one of the kinases involved in the inflammatory response [115,116]. The phosphoinositide 3 kinases (PI3K)-Akt axis improves to differentiate helper T-cell subsets [117]. The phosphorylation of a variety of downstream effector molecules by AKT is involved in cell growth, metabolism, and survival [117]. AKT enhanced FOXP3 gene expression in Tregs, resulting in Tregs with a stable phenotype and functions [117].

Both Th1 and Th17 cells have been found to play a role in the initiation and progression of myocarditis [118–120]. Tregs produce IL-10, which reduces the severity of CVB3-induced viral myocarditis by suppressing the release of Th17-related cytokines (IL-17A and IL-6) [119]. In addition, IL-10 inhibited the immune response by lowering MHC II complexes and B7 family co-stimulatory molecules on antigen-presenting cell surface, including dendritic cells and macrophages [111,119].

Treg impairments were detected in CAD patients due to the decrease in Treg frequency and downregulation of FOXP3, IL-10, and TGF-β gene expressions and higher IFN-γ and hsCRP levels [121]. Increased apoptosis induced by inflammation and oxidative stress was also a cause of Treg impairment [121]. In the angiotensin-II-induced hypertension model, Treg deficiency was attributed to increased pro-inflammatory factors like IFN-γ and IL-17A [122]. These cytokines play a part in the synthesis and degradation of vasoconstrictors and vasodilators and the expression of Angiotensin-II, which contributed to artery inflammation and high blood pressure [123]. It was shown that the transfusion of Tregs reduced heart hypertrophy, fibrosis, and arrhythmia in the angiotensin-II-induced hypertension model [124–126].

Myocardial infarction (MI) happens when blood flow to a part of the

heart is inhibited or interrupted, resulting in injury to the cardiac muscle [127]. A decreased percentage of circulating Tregs has been associated with a higher risk of heart failure hospitalization, inversely correlated to IL-6 levels [127]. Transfusion of Tregs improved infarct size and left ventricular dilation in a mouse model of myocardial infarction [128]. Inflammatory myeloid cells such as neutrophils, monocytes, and T cells increased in the infracted myocardium in this model [128]. It was found that Tregs may affect myeloid cell infiltration by modulating the expression of chemokines, which is involved in homing of inflammatory cells [129]. TNF-α and IFN-γ secretion by infiltrated cells has been indicated to induce M1 macrophage polarization [130,131]. M1 macrophage potentially has adverse effects on inflamed myocardium by releasing pro-inflammatory cytokines (IL-1, IL-6, IL-12, and TNF-α), chemokines (MCP-1, CXCL1-3, CXCL5, and CXCL8-10), high levels of inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS) which all attribute to enhance the inflammatory responses in inflamed myocardium [130,131]. Interestingly, Tregs improved M2-like monocyte differentiation post-MI by producing IL-10, TGFβ, and IL-13 *in-vivo* and *in-vitro* [132]. As a result, cardiac healing after MI was improved [133,134]. Activated M2-like macrophages released anti-inflammatory cytokines such as IL-10, IL-13, and TGF-β that are essential in wound healing, tissue remodeling, and angiogenesis [135,136]. Monocytic cells released osteopontin in response to TGF-β and IL-10 [132]. In the healing myocardium, osteopontin significantly impacts collagen production and matrix assembly [137].

7. The potential of Treg therapy in reducing cardiovascular complications in COVID19 patients

7.1. The probable role of Tregs in alleviating cardiovascular complications in COVID-19

At a glance at previous sections, however, a variety of immune responses have been identified in COVID-19 infection [138], the immunological alternations primarily trending to an anti-inflammatory state (Th2 and Tregs) neutralized COVID-19 inflammatory reactions (cytokine storm) [134]. Current studies showed that the frequency of peripheral Tregs fundamentally diminished in patients with severe COVID-19 infection [61,72,92]. Tregs impairment can lead to cytokine storm since Tregs regulate inflammatory responses [61,72,92]. Cardiovascular complications in COVID19 patients are caused by a hyper-inflammation state in the cytokine storm, which causes elevated myocardial oxygen consumption, endothelial dysfunction, and suppressed cardiac activity [140,141]. Additionally, the autopsy revealed increased mononuclear cell infiltration through the myocardium in COVID-19 patients with cardiovascular complications, indicating the increased inflammatory responses in the heart tissue [62].

Here, we propose that Tregs may decrease the severity of cardiovascular complications in COVID-19 patients. Tregs, control immune responses especially inflammatory responses of Th17 and Th1 cells [142,143]. This could be due to the interaction of surface markers of Tregs including, PD-L1, CD25, and CTLA-4, with the ligands on the target cells or/and the secretion of TGF-β and IL-10 (as the tolerogenic cytokines) that stimulate apoptosis and inhibit the cytotoxicity of Th1 and Th17 cells [144–146] (Fig. 2). As noted, Th1 and Th17 cells could exacerbate inflammatory conditions in cardiovascular diseases through secreting inflammatory cytokines, including IFN-γ, IL-17A, and IL-6, which may play a role in cytokine storm and the pathogenesis of severe COVID-19. Furthermore, these cytokines regulated the synthesis and destruction of vasoconstrictors and vasodilators, leading to increased blood pressure [123]. Therefore, Tregs may control inflammatory reactions and blood pressure, reducing the severity of cardiovascular complications associated with COVID-19 infection.

In another aspect, Tregs are critical in controlling endothelium-dependent relaxation in coronary arterioles and arterial blood pressure [100]. Endothelial cells regulate vascular tone and aortic stiffness (one reason for high blood pressure) by releasing relaxing factors like prostacyclin and nitric oxide [131,147]. Of note, SARS-CoV-2 can infect vascular endothelial cells [148,149]. Emerging evidence indicates that endothelial dysfunction and arterial hypertension are the critical characteristics of COVID-19 infection [150–152]. This includes the involvement of vascular endothelium in leukocyte attraction, which leads to cytokine secretion and tissue damage, both of which are key elements in ARDS, and cardiovascular complications [150–152].

It was discovered that transferring Tregs into hypertensive mice lowered arterial blood pressure and boosted endothelium-dependent relaxation in coronary arterioles by minimizing inflammatory cytokines and macrophage infiltration [151,152]. Mechanistically, it may result from releasing IL-10, TGF-β, and IL-35 in a paracrine-dependent manner [153]. In addition, these cytokines may reduce oxidative stress by inactivating NOX, which controls endothelium-dependent relaxation [152]. As a result, it is reasonable to hypothesize that Tregs could reduce the severity of COVID-19 infection by increasing endothelial function and lowering high blood pressure, both of which are induced by COVID-19 infection.

Tregs have been found to reduce viral load, limit antiviral immune responses, and prevent myocarditis by regulating inflammatory responses [103,111]. Tregs also have been shown to modulate Th1 and Th17 cells by releasing IL-10, suggesting that Tregs may be able to prevent myocarditis in COVID-19 patients [118–120]. Mechanistically, Tregs suppressed p38 MAP kinase activation and increased Akt activation (Fig. 2) by secreting TGF-β [112,113]. As a result, it's not unexpected that TGF-β is involved in neutralizing adverse immunological responses; Akt activation, p38 inhibition, and immune control by Tregs would all be anticipated. This likely resulted in a reduced viral load and immune infiltration in the case of COVID-19 infection.

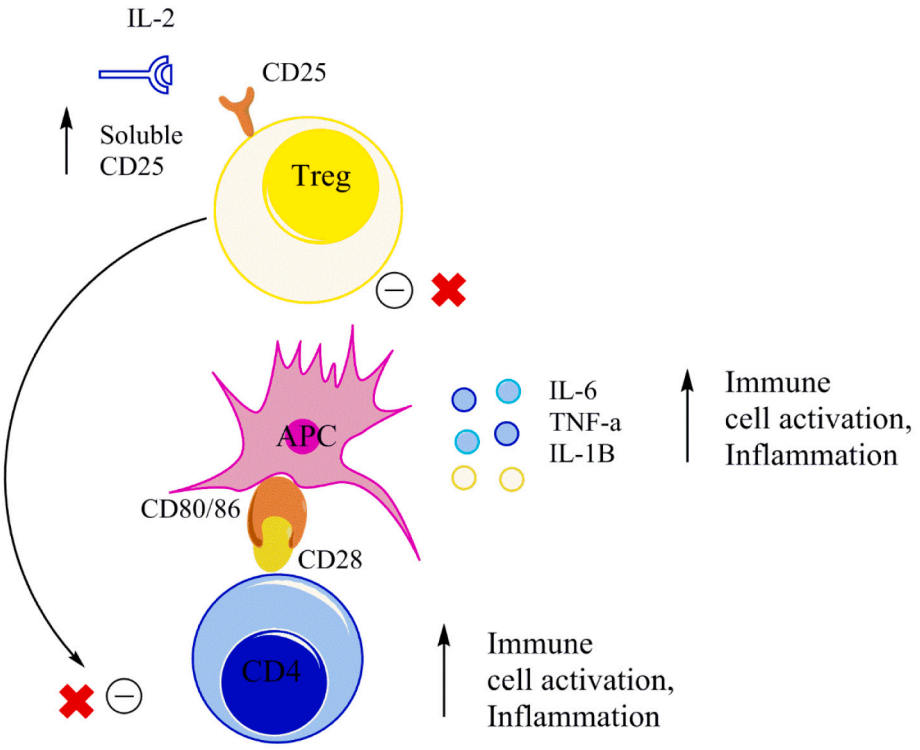
In COVID-19 patients, myocardial infarction has been associated with heart failure [154]. Tregs may enhance wound healing in COVID-19 patients with myocardial infarction by influencing macrophage differentiation. Tregs may promote M2-like monocyte differentiation after myocardial infraction by secreting TGF-β, IL-13, and IL-10 in fractioned myocardium *in vivo* and *in vitro* [132–134]. TGF- also promoted collagen deposition by myofibroblasts and accelerated the formation of scar tissue [155]. In addition, TGF-β, and IL-10, as previously discussed, can cause monocytes and macrophages to produce osteopontin [132].

Osteopontin is a glycoprotein with various activities, including cell adhesion and migration, and it contributes to matrix assembly and wound healing following myocardial infarction [137,142]. Therefore, it's intriguing to suggest that Tregs may have a role in accelerating extracellular matrix deposition and cardiac healing in patients with severe COVID-19 by increasing collagen and osteopontin levels.

7.2. Therapeutic opportunities for Tregs in cardiovascular complications associated with severe COVID-19

Tregs, as noted previously, may reduce the severity of cardiovascular complications in COVID-19 patients. Therapeutic interventions for enhancing tolerance based on the adoptive transfer of Tregs are an effective strategy to treat Treg-mediated diseases, including autoimmunity, spontaneous abortion and, tissue transplantation [156,157]. This includes isolating *in vivo* differentiated Tregs, expanding Tregs *ex vivo*, or generating iTreg cells *in vitro* and subsequent transfer into the body [156,157]. This strategy could be used to treat cardiovascular complications caused by severe COVID-19 infection. To utilize Treg immunotherapy, meticulously designed clinical trials and precise Tregs expansion planning need to be employed, using the newest scientific technologies in Treg biology in COVID-19 treatment. In addition, probable adverse effects of artificially reinforcing Tregs, including diminished immune surveillance against tumors, need to be considered. Another issue that needs attention is the appropriate dose and subsets of Tregs [157]. The critical challenges for utilizing Treg therapy in treating cardiovascular complications in severe COVID-19 are the diagnosis of

A. Tregs impairment in severe COVID-19



B. The machanism actions of Tregs in reducing cardiovascular complications

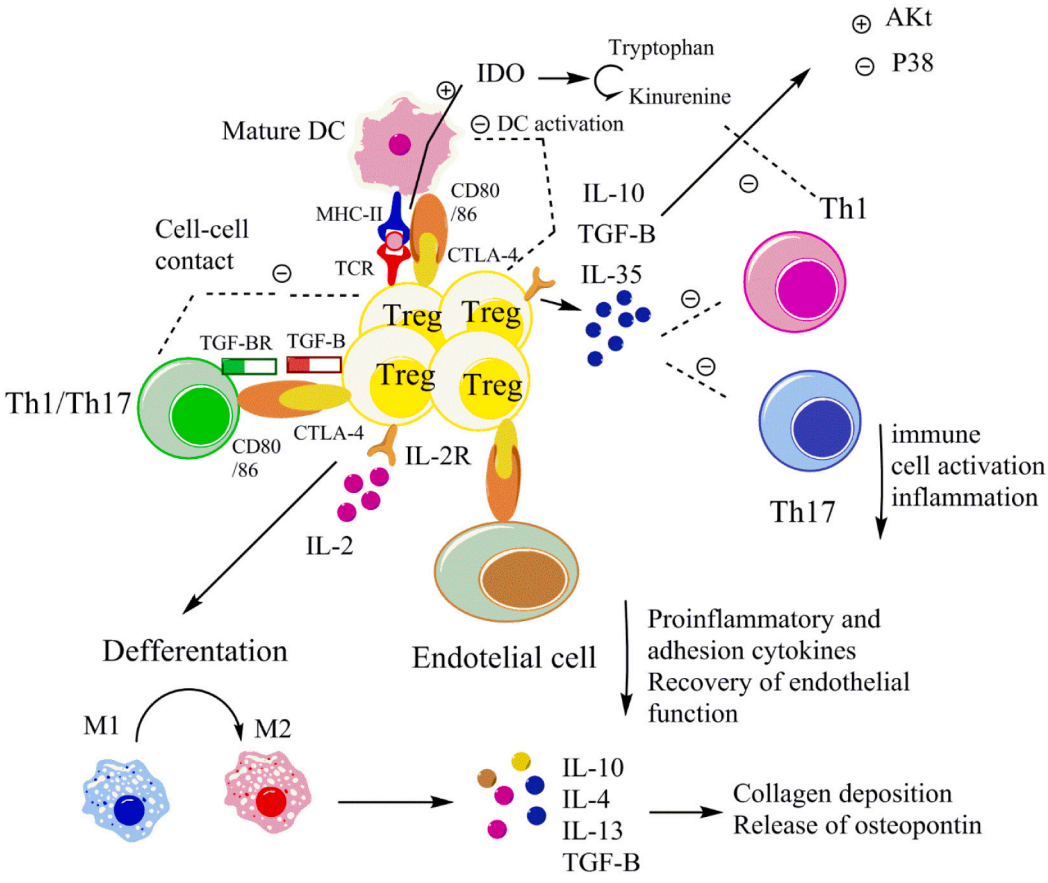


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Fig. 2. A- Tregs impairment in severe COVID-19. B- Proposed mechanisms of actions of Tregs in alleviating cardiovascular complications in COVID-19. Tregs regulate Th17 and Th1 cell inflammatory activation by molecular interactions (like CD25 and CTLA-4 with ligands on target cells), TGF-β, and IL-10 secretion (as the tolerogenic cytokines). Tregs may enhance cardiac wound healing *via* activating M2 macrophages, reducing p38 MAP kinase, and increasing Akt activation. Notably, IL-10 and TGF-β could accelerate extracellular matrix deposition and cardiac healing by enhancing collagen deposition and triggering osteopontin release from monocytes and macrophages.

Treg cell deficiency and determining the appropriate time of adoptive transfer of Tregs. To our knowledge, the investigation of Treg cell deficiency in patients with severe COVID-19 was not the primary endpoint of any of the studies. The establishment of a standardized concept of minimum necessary Treg markers will be a good step.

8. Concluding remarks and future directions

Tregs are the key regulators of immune responses. Multiple pathways for controlling immune reactions have been proposed, emphasizing the anti-inflammatory properties of Tregs. Uncontrolled inflammation has been demonstrated in the pathogenesis of COVID-19, which may be related to a reduction in the frequency of Tregs and functions in severe COVID-19 infection. As a result, COVID-19 patients suffer from severe lung injury and cardiovascular complications, the leading causes of morbidity and mortality.

Tregs cell therapy is widely used to treat various autoimmune and inflammatory diseases in animal models, and some clinical trials are going on. Rigorously designed clinical trials and detailed Tregs manufacturing planning should be considered for evaluation in clinical trials to evaluate their effectiveness in improving clinical outcomes and reducing cardiovascular compilations of patients with severe COVID-19. In this light, we propose that the adoptive transfer of autologous Tregs may be one option for treating patients with severe COVID-19 with cardiovascular compilations. However, the dosage of Tregs and complementary therapies for SARS-CoV-2 infection must be approached. Furthermore, the probable adverse effects of artificially reinforcing Tregs, including diminished immune surveillance against tumors, need to be taken into account. As we proposed in previous research, adoptive transfer of Tregs could be an important clinical approach for disorders with inflammatory roots, such as spontaneous abortion. According to the current evidence, we suggest that controlling inflammatory responses and improving endothelial and atrial function, lowering high blood pressure, lowering the viral load and limiting adverse antiviral immune responses, as well as improving cardiac healing are the possible beneficial effects of adoptive transfer of Tregs in alleviating cardiovascular complications including, myocarditis, CAD, hypertension, myocardial infarction and cardiac failure in COVID-19 patients. According to the new findings, we also propose for adoptive transfer of Tregs, expansion of autologous Tregs in the presence of vitamin C + RA established a population that was more stable when exposed to an inflammatory, suggesting a possible strategy for reducing Treg plasticity in inflammatory conditions like in COVID-19 infection.

Mechanisms of actions of transferred Tregs may be mediated at the molecular and cellular levels. Tregs regulate the function of pro-inflammatory cells such as Th17 and Th1 cells and mononuclear cell infiltration through molecular interactions (PD-L1, CD25, and CTLA-4 with ligands on target cells), and the secretion of TGF-β and IL-10 (as the tolerogenic cytokines). Adoptive transfer of Tregs may enhance cardiac wound healing *via* activating M2-like, reducing p38 MAP kinase, and increasing Akt activation. Additionally, by enhancing collagen deposition and inducing osteopontin release from monocytes and macrophages, IL-10 and TGF-β may accelerate extracellular matrix deposition and cardiac healing.

Nutrients with immune-modulatory properties that boost Tregs differentiation, proliferation, and functions like vitamin D, vitamin A, niacin and, short-chain fatty could be the natural solution in this scenario. As we indicated, VitD3 could enhance the frequency and functions of Tregs (FOXP3 and GITR) [143,158–160]. Statin drugs, which are known to have immunomodulatory activities and induce Tregs [161,162], have also been shown to be associated with reduced COVID-19 outcomes including mortality [163–165]. Furthermore, in future studies, the role of antiviral drugs such as valproic acid, which has been shown to have beneficial effects on Tregs, can be investigated in reducing cardiovascular risks in COVID-19.

In conclusion, the physiological advantages of Tregs and Treg adoptive transfer are exciting research and clinical fields to investigate the cellular, molecular, and immunological mechanisms that contribute to the treatment of cardiovascular complications in severe COVID-19. Therefore, potential clinical trials that could pave the way in reducing cardiovascular complications in patients with severe COVID-19 are recommended.

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CRediT authorship contribution statement

Nafiseh Saghafi - **participate with the conception**, **study design**, **drafting the manuscript**.

Seyed Abdolrahim Rezaee - **involved with the study design**, **critical revision**, **editing and approval of the final draft of the study**.

Amir Abbas Momtazi-Borojeni - **contributed with the study design**, **critical review**, **editing and the support of the final draft**.

Fataneh Tavasolian - **contributed with the conception**, **study design**, **critical revision**, **editing and the final approval of the manuscript**.

Elham Abdollahi - **contributed with the study design**, **critical review**, **editing and the support of the final draft**.

Thozhukat Sathyapalan - **contributed with the conception**, **study design**, **critical revision**, **editing and the final approval of the manuscript**.

Amirhossein Sahebkar - **contributed with the conception**, **study design**, **critical revision**, **editing and the final approval of the manuscript**.

Declaration of competing interest

A conflicting interest exists when professional judgment concerning a primary interest (such as patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It may arise for the authors when they have financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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