Management of COVID-19 Related Myocarditis: A Systematic Review

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ABSTRACT

On January 7 in China, one patient was identified with a new corona virus in throat culture, and World Health Organization called it severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Herein, we aimed to summarize overall data for COVID-19 disease related myocarditis and its treatment. In the initial stages, patients developed symptoms of severe acute respiratory infection and afterwards other serious symptoms such as septic shock, metabolic acidosis, coagulation disorders, multiple organ failure problems developed. Complications were mostly associated with pneumonia (91.1%) and acute respiratory distress syndrome. Before the Coronavirus Disease 2019 (COVID-19) infection, the presence of cardiovascular diseases has been found to increase the severity and side effects of primary respiratory syndrome. Since management of COVID-19 related myocarditis is crucial, 114 publications indexed in Pubmed between Dec 10, 2019 and October 16, 2020 were scanned extensively in this review in order to summarize the treatment options of COVID-19 related myocarditis. Analysis of 44.672 COVID-19 cases showed an increased risk of mortality in elderly people (14.8% for patients over 80 years old) and patients with cardiovascular disease (10.5%). Patients with diabetes (7.3%) and hypertension (6%) also demonstrated an increased risk of mortality. The rate of underlying chronic respiratory disease was 6.3%. Arrhythmia was found in 16.7% and acute heart injury existed in 7.2% of 138 hospitalized COVID-19 patients. ACE inhibitors or ARBs should be administered in patients with wall motion abnormality or heart failure with reduced EF. Diuretics should be considered in patients with volume overload and torsemide should be preferred as first option. Non-steroidal antiinflammatory drugs and cardiac glycosides should be avoided. Physical activity should be restricted until the disease resolved. IVIG and interferon therapy are feasible treatment options with reasonable side effect profile.

Key words: COVID-19; Myocarditis; Arrhythmia; Diuretics; Systematic Review

INTRODUCTION

On January 7 in China, one patient was identified with a new corona virus in throat culture, and World Health Organization (WHO) called it severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In the initial stages, patients developed symptoms of severe acute respiratory infection and afterwards other serious symptoms such as septic shock, metabolic acidosis, coagulation disorders, multiple organ failure problems developed.[1,2] Complications were mostly associated with pneumonia (91.1%) and acute respiratory distress syndrome.[3,4] In the 2020 report prepared by the China Medical Treatment Group for Coronovirus Disease 2019 (COVID-19), it was reported that during hospitalization, fever up to 88.7%, cough in 67.8%, then dry cough, headache, fatigue or shortness of breath.[5]

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Before the COVID-19 infection, the presence of cardiovascular diseases has been found to increase the severity and side effects of primary respiratory syndrome.[6] Analysis of 44.672 COVID-19 cases showed an increased risk of mortality in elderly patients (14.8% for patients over 80 years old) and diabetes (7.3%), hypertension (6%) and cardiovascular patients (10.5%). The rate of underlying chronic respiratory disease was 6.3%.[7] Arrhythmia was found in 16.7% and acute heart injury in 7.2% of 138 hospitalized COVID-19 patients.[8] In one study, 23.0% of patients with COVID-19 infection had heart failure. Heart failure was higher in patients who lost their lives than the survivors (51.7% vs. 11.7%). The reason for this is unknown whether heart failure deaths occurred due to new cardiomyopathy (myocarditis or stress cardiomyopathy) or pre-existing left ventricular dysfunction.[9]

Troponin is the most specific laboratory finding of injury due to myocarditis, acute coronary syndrome, or myocardial injury. In one study, 20% of died patients had cardiac injury characterized by high sensitive troponin (Hs-troponin) levels. In the multivariable adjusted model, cardiac injury was significantly and independently linked to mortality (hazard ratio: 7.89).[10] In the another study, in multivariate logistic regression analysis, high cTnI (OR = 26.909, 95% CI 4.086-177.226, P = 0.001) and coronary artery disease (OR = 16.609, 95% CI 2.288-120.577, P = 0.005) was found as independent risk factors for critical disease.[11]

In a study involving 187 patients with COVID-19, troponin levels and mortality rates were higher in patients using angiotensin converting enzyme inhibitor (ACEI) / Angiotensin receptor blocker (ARB) than those who did not ([21.1%] vs [5.9%], [36.8%] and [25.6%]). In patients with high plasma TnT levels, who were eventually discharged or died, mean duration time of the disease from onset to discharge or death (IQR) was 28 (22-33) and 23.5 (18.25-34.5) days, respectively. Patients with hypertension (63.5% vs 20.7%), coronary heart disease (32.7% vs 3.0%), cardiomyopathy (15.4% vs 0) and diabetes(30.8% vs 8.9%) had higher TnT levels.[12]

The obvious relationship between TnT levels and C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels indicates that myocardial injury is associated with the severity of inflammation and ventricular dysfunction. Acute respiratory distress syndrome (ARDS), malignant arrhythmias, acute renal injury, and acute coagulopathy were more common in those with high TnT levels. It was found that the increase of these three parameters was related to the poor prognosis and the decrease was related to the good prognosis. In patients with cardiovascular disease and troponin increase,

death rate was 69%, in those without cardiovascular disease and troponin increase, death rate was 37%, and in those with cardiovascular disease and normal troponin level, the mortality rate was 13%. Acute myocarditis, in addition to acute coagulopathy, could explain cases of sudden cardiac death observed during quarantine among COVID-19 patients not admitted to hospital.[12]

CORONAVIRUSES

Coronaviruses (CoVs) are single-stranded positive-sense RNA viruses, comprises of a large family of viruses that are common in human beings as well animals (camels, cattle, cats, and bats). CoVs are named for crown like spikes on their surface and belong to the Coronavirinae subfamily, which are further classified into four genera: the α, β, γ, and δ CoVs by phylogenetic clustering, of which α and β are known to cause infection in humans.[13]

At the end of 2019, the first pneumonia cases of unknown origin were identified in Wuhan, a city in the Hubei Province of China.[14] The pathogen has been identified as a novel enveloped RNA betacoronavirus that has currently been named as SARS-CoV-2, which has a phylogenetic similarity to SARS-CoV.[15] It rapidly spread, resulting in an epidemic throughout China and then gradually spreading to other parts of the world in pandemic proportions. In February 2020, the World Health Organization designated the disease COVID-19, which stands for corona virus disease 2019.[16]

Transmission of SARS CoV-2 seems to be primarily from person to person via close contact and through respiratory droplets. The exact incubation period is not known.[17,18] It is presumed to be between 2 to 14 days after exposure, with most cases occurring within 5 days after exposure.[19] These values should help inform COVID-19 case definitions and appropriate quarantine durations.

People with COVID-19 have had a wide range of symptoms reported–ranging from mild symptoms to severe illness. The three primary symptoms of COVID-19 are fever, cough, and shortness of breath or difficulty breathing. Less common symptoms are muscle pain, anorexia, new loss of taste or smell, sore throat, nasal congestion, and headache. These symptoms may appear in as few as 2 days or as long as 14 days after exposure.[20] Also, gastrointestinal symptoms, such as diarrhoea, abdominal pain, and vomiting, have been reported in 2% to 10% of patients with COVID-19.[21]

Diagnosis is currently through SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction diagnostic panel using upper and lower respiratory specimens.[22] New

serologic tests, at-home test kits, and point-of-care tests are likely to become available in the near future.

COVID-19 mainly affects the respiratory tract and can progress in severe cases to pneumonia, acute respiratory distress syndrome and multi-organ failure. With the increasing number of infected cases, COVID-19 has been shown to cause cardiovascular injury, in addition to typical respiratory symptoms. This condition can, in fact, cause significant myocardial injury, which worsens the disease and affects the prognosis.

PATHOGENESIS AND DIAGNOSIS

The virus binds to the ACE2 receptor with the Spike (S) glycoprotein of SARS-CoV-2 and enters the cell. SARS-CoV-2 primarily occupies the alveolar epithelial cells and creates respiratory symptoms.[23] The ACE2 receptor is retained by some coronaviruses, its primary physiological role is the maturation of angiotensin, a peptide hormone that controls vasoconstriction and blood pressure. ACE2 is a type I membrane protein that is expressed in the lungs, heart, kidneys, and intestine. Decreased ACE2 expression is associated with cardiovascular diseases.[24]

Viral myocarditis and injury mechanisms are uncertain. Possible mechanisms are discussed.

1. Increased heart load: In viral infections, the load of the heart increases about 4-8 times as much as in important exercises. It can decrease cardiac functions in pneumonia, infection-induced increase in metabolic demand and reduced cardiac reserve.

2. Increased expression of Angiotensin Converting enzyme 2 (ACE2): Because ACE2 is involved in lung protection, binding of the virus to this receptor contributes to viral pathogenicity.[25] ACE2 expression is increased in the lung, although it is not certain, it has been accused of higher levels of ACE2 in myocardial injury. The severity of the disease in those with cardiovascular diseases, relative to healthy individuals, may be associated with increased ACE2 secretion in these patients.[26] It has been stated that there is an increase in ACE2 expression especially in pericytes in myocardium of heart failure patients and therefore, these patients may be more sensitive to SARS-CoV-2 infection.[27]

3. Excessive inflammation: Excessive inflammatory cell infiltration was detected in the alveoli of patients who developed acute respiratory distress syndrome due to SARS-CoV-2 infection.[28] Excessive inflammatory activity by SARS-CoV-2 can be suppressed with corticosteroids. Therefore, it has been stated that exaggerated inflammation may be responsible for viral injury, this explains the extensive corticosteroid use in critical COVID-19 patients.[29] The patients who died had higher levels of troponin, myoglobin, C-reactive protein, serum ferritin, and interleukin-6, so it was thought that myocarditis-related cardiac events were likely to occur due to the high inflammatory load.[30] Stimulating excessive cytokine release by type 1 and 2 T helper cells. HsCRP and cytokine levels were found to be associated with cardiovascular risk.

4. Hypoxemia: Hypoxemia and respiratory dysfunction harm myocardial cells. Respiratory acidosis increases loading of the right ventricle which results in tachycardia, increased wall stress, and extend of tissue damage.

5. Coronary plaque destabilization and procoagulation: Destabilization of coronary artery plaques occur due to inflammation. In patients with coronary artery disease and heart failure, there is a risk of coronary plaque rupture secondary to the virus-induced systemic inflammation. Vascular inflammation creates endothelial dysfunction and an increased state of coagulation.[31,32] Pro-coagulating effects of systemic inflammation may also increase the risk of stent thrombosis.[33] The tendency to type 2 myocardial infarction increases due to infection induced myocardial demand.[34]

6. Direct effect on myocard: In a study conducted in 2009, 35% of patients with severe acute respiratory syndrome due to SARS-CoV infection had a virus genome in the heart, suggesting the possibility of direct damage to the virus.[35] SARS-CoV-2 may have the same mechanism as SARS-COV because it is highly homologous in 2 virus genomes.[36,37] COVID - 19 RNA has been detected in the small and large intestine, lymph nodes, spleen, liver, heart, kidney, skeletal muscle, adrenal gland and cerebrum as a result of extrapulmonary spread.[38] The pathogenesis of SARS-CoV-2-related cardiac involvement can be related to the proliferation and spread of the virus from the blood or respiratory system lymphatic system. There is ACE2 receptors in the vascular endothelium and myocard, the possibility of virus damage to the endothelium and myocardium.[39]

7. Immune function weakness: There are common mechanisms that lead to CVD and regulation of immune function. Age is the strongest risk factor for CVD, and is important for susceptibility and severity to COVID-19.[40]

Although the symptoms are mostly respiratory, cardiac involvement may occur as a late finding. Cardiac involvement, as shown in the autopsy study, may be subclinical with several inflammatory cells, or significant

cardiac manifestations may be detected without respiratory symptoms. Many viral infections, such as influenza and parvovirus B-19, which have myocardial involvement, have been identified.[41]

Necrosis and eventually ventricular dysfunction occurs in myocarditis caused by focal or global myocardial inflammation. Patients develop chest pain after an influenza-like syndrome. There may be signs of acute coronary syndrome in electrocardiography or laboratory tests. However, obstructive coronary artery disease is not detected in coronary angiography. Focal myocarditis is often suspected with wall motion disorders and clinical evidence.[42]

The cardiac findings first described in COVID-19 infection were palpitations and chest pain.[43] Other published and anecdotal reports include myocarditis, cardiac arrest and acute heart failure. There may be symptoms of chest pain, dyspnea, palpitations, fever, tachycardia and depending on severity hypotension and low oxygen saturation, heart failure symtomps and shock. In patients with atypical chest pain and minimal respiratory distress, increased troponin levels may be a stimulant for acute myocarditis.[44,45]

Since magnetic resonance and endomyocardial biopsy are not always used in COVID-19 patients, the frequency of acute myocarditis was reported as 12.5% in a patient series based on elevation of troponin level, electrocardiogram (ECG) (ST/T segment changes),transthoracic echocardiography (TTE) (wall motion abnormalities, left ventricular ejection fraction (LVEF) < 50, LV wall thickening >10 mm and/or pericardial effusion) findings. The most common echo finding was pericardial effusion and the frequency of arrhythmia was 16%.[46]

There is limited information about cardiac involvement due to SARS-CoV-2 infection. The examinations suggested in the scarce literature for COVID-19 myocardial injury or myocarditis is listed below.

Swabs: Nasopharyngeal and oropharyngeal swabs (for reverse transcriptase polymerase chain reaction assay)

Lab: Greater leukocyte counts, lenfopenia, high-sensitivity troponin T,NT-proBNP, C-reactive protein, creatine kinase, myoglobin, procalcitonin, D-dimer, ferritin

Chest X-ray: Opacities,infiltration,etc.

ECG: ST depression, elevation, arrhythmia, tachycardia, QTc meauserement (>500ms),etc.

Chest Computed tomography (CT): Especially ground-glass opacity; in early chest computed tomography, it was reported that 85% of patients had findings, and 75% of patients had ground-glass opacity and consolidation in the subpleural and peripheral areas.[47] CT also rules out acute life-threatening clinical settings such as aortic dissection, pneumothorax and pulmonary embolism.

TTE: hypokynesis, dilatation, effusion, etc.

Coronary CT angiography: It is recommended to rule out coronary artery disease (CAD),

Cardiac magnetic resonance (CMR): Myocardial edema, pseud-hypertrophy, late gadolinium enhancement sequences for detectable myocardial scar/necrotic foci, etc.

Endomyocardial biopsy (EMB): T-lymphocytic inflammatory infiltrates, interstitial edema, foci of necrosis, fibrosis, viral particle detection.

Molecular analysis: Used for SARS-CoV-2 genome within the myocardium.

The number of case reports on myocarditis is increasing. One patient had SARS-CoV-2 positivity in nasopharyngeal and oropharyngeal swabs. Diffuse T-lymphocytic infiltration (CD3 +> 7 / mm2), diffuse interstitial oedema and limited necrosis areas were detected in endomyocardial biopsy. SARS-CoV-2 genome was not able to be detected in the myocardium in the molecular analysis. Thus, acute virus-negative lymphocytic myocarditis has been diagnosed.[48]

EMB was performed in a SARS-CoV-2 patient who recovered after development of sudden cardiogenic shock. Low-grade interstitial and endocardial inflammation, large (> 20 μm) vacuole, CD68 - positive macrophages, membrane damage and cytoplasmic vacuoles were detected in pathologic examination. Typical viral particles of 70-120 nm in size were detected in cytopathic interstitial inflammatory cells. No viral particles were detected in myocytes.This is thought to be the result of either the extra-pulmonary spread of infected alveolar macrophages or viremic phase.[49]

As our experience of this epidemic increases, which we are still trying to understand, questions regarding myocardial injury can be fully answered. Myocarditis is identified as inflammation of heart muscle cells. The causes of inflammation can be external antigens such as viruses, bacteria, parasites, toxins and drugs or internal triggers such as autoimmune activation against self antigens. The diagnosis of myocarditis is diffucult, as it requires endomyocardial biopsy. Therefore it is hard to truly detect the incidence of cardiac involvement. The Dallas criteria are used for histopatologic diagnosis:

- Myocarditis: Presence of inflammatory cells and myocyte necrosis findings on the same microscopic section.
- Borderline myocarditis: Presence of inflammatory cells infiltrates without of necrosis.
- No myocarditis: There are no inflammatory cells and necrosis.[50-51]

CLINICAL PRESENTATIONS AND PHYSICAL EXAMINATION FINDINGS

Clinical presentation of myocarditis may be asymptomatic or may be with chest pain. The chest pain mostly relates with acute pericarditis and rarely associates with coronary artery vasospasm. In patients with myocarditis, arthralgias, malaise, fever, sweats, chills can occur at the same time with myocarditis or before the myocarditis. When heart failure occurs, the main symptoms are dyspnea, fatigue, edema. In some patients who have heart failure, fatigue and decresead functional capacity are initial symptoms. In some cases, arrhytmias can be seen which cause syncope, tachyarrhytmia or sudden cardiac death. These symptoms are similar in patients with COVID-19 myocarditis.

Acute decompensated heart failure signs mostly include an S3 gallop, central and peripheral edema, juguler venous distention, tachycardia. If acute pericarditis accompanies, pericardial friction rub may be audible.[50,52-54]

LABORATORY EVALUATION

In these patients, C reactive protein(CRP), erytrocyte sedimentation rate(ESR),procalcitonin white blood count levels are high. When myocardial injury accompanies, troponin T (TnT) or I, creatin kinase (CK) CK-MB, myoglobin N terminal pro B type natriuretic peptide(NT-proBNP) level increase. Guo et al. found in their study that TnT levels are significantly associatedwithlevels of C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP), thus linking myocardial injury to severity of inflammation and ventricular dysfunction.[55]

In ECG of these patients, there are nonspesific ST-T changes, T wave abnormalities, sinus tachycardia. Occasionally, ST elevation is seen in ECG, when pericarditis accompany myocarditis. I to III degree atrioventricular block, left bundle brunch block, sinus arrest, ventricular fibrillation or tachycardia, asystole, atrial fibrillation, reduced R wave height, abnormal Q wave, low voltage, premature beats can also be seen.

TTE is another diagnostic tool. In echocardiography, regional or global wall motion abnormalities, ventricular dilatation, pericardial effusion, intracardiac thrombus can be established. Also, coronary angiography can be done to exclude coronary artery abnormalities.

Lastly, CMR can be chosen to diagnose myocarditis. In CMR, edema can be established. Late gadolinium enhancement which is classical myocarditis pattern can be identified.[53,54]

TREATMENT OF SARS-COV-2 RELATED MYOCARDITIS

There are only case reports in the literature about SARS-CoV-2 related myocarditis. Hence the beginning of SARS-CoV-2 outbreak is recent, there are not enough trials and data about the treatment of SARS-CoV-2 related myocarditis. Therefore; there are not any specific treatment options for SARS-CoV-2 related myocarditis and management is based on constitutively traditional viral myocarditis treatment.

Heart failure therapy

Most of the cases with viral myocarditis are asymptomatic and heart failure develops in a small proportion of cases.[56] Patients with heart failure or wall motion abnormality should be treated by the lights of current heart failure gudelines to prevent from irreversible myocardial remodelling.[57] ACEIs and ARBs are the indispensible part of the treatment. In mice and rat models; it is demonastrated that kaptopril, olmesartan and losartan reduced inflammation, necrosis, and fibrosis in experimental virus induced myocarditis models.[58,59]

Diuretics should be used in patients with the symptoms and signs of hypervolemia. Torsemide has additional beneficial effects than furosemide. Torsemide reduced the progression of myocarditis in a rat model by decreasing fibrosis, myocyte sizes, and myocardial protein levels of transforming growth factor-beta-1, collagen III, and aldosterone synthase.[60]

Beta-blockers improveventricular function and reduce hospital admission due to worsening heart failure. Usage of beta-blockers in myocarditis is associated with better survival and it is known that lack of beta-blocker treatment is associated with poor outcomes.[61] Carvedilol has antioxidant properties in addition to its beta receptor blocking effect and it is shown that carvedilol decreases inflammatory response in experimental rat models while metoprolol and propronalol did not havesuch immunomodulating effects.[62] On the contrary; metoprolol administration significantly increased inflammation and necrosis as well as mortality in murines with Coxsackievirus B3 myocarditis.[63] Beta-blocker

treatment should be avoided in patients with hemodynamic instablity and acute decompansated heart failure.[57]

Aldosterone antagonists are recommended in patients with heart failure whose functional capacity is still NYHA II-IV despite treatment with beta blocker and ACE/ARB combination. Aldosterone antagonists reduce recurrent hosptalisation and improve survival rate in heart failure with reduced EF.[57] Eplerenone has additional anti-inflammatory effects by inhibiting mast cell-derived proteinases.[64] Aldosterone antagonists should not be administered in ealy phases of myocarditis and it should be considered if firstline heart failure treatment failed.

Cardiac glycosides are used in patients with HF to improve functional capacity and reduce rehospitalization. However, glycosides causes increase in myocardial work and exaggeretes production of myocardial pro-inflammatory cytokines. Glycosides may also limit the maximal tolerated beta blocker dose.[65] Therefore, cardiac glycosides should be avoided in patients with myocarditis.

Calcium channel blockers are not recommended in heart failure due to their negative inotropic effects. In mice models amlodipine reduced nitric oxide levels resulting with decreased myocardial damage. In another animal study including rats with experimental autoimmune myocarditis, pranidipine and amlodipine improved left ventricular functions.[66,67]

Non-steroidal antiinflammatory drugs are mainstay of pericarditis treatment but they should be avoided in viral myocarditis. Indomethacin and NSAIDs caused increased inflammation and mortality rates in murine models of acute viral myocarditis.[68,69] Asetylsalicylic acid administration is also shown to be associated with increased mortality.[70]

Restriction of physical activity

Aerobic physical activity should be avoided in patients with acute myocarditis. Sustained exercise leads both immunsupression by inhibiting T cell functions and increased mortality.[71] Duration of the activity restriction should last till the disease completely resolved. Physical activity should be delayed at least 6 months and physical activity should be permitted after detailed cardiologic evaluation in elite athletes.[72]

Arrhythmia management

All types of arrhythmias may develop during acute myocarditis. Advanced atrioventricular (AV) blocks and symptomatic bradycardia episodes should be treated with temporary pacemaker implantation. Complete heart block or ongoing advanced AV block despite the resolution of acute phase of myocarditis are indications of pacemaker implantation. ICD (Implantable Cardioverter Defibrillator) implantation should

be considered in patients without documented malignant arrhythmia if the functional capacity is NYHA II-IV and LVEF <35% despite 3 months of optimal medical treatment. In patients with cardiac arrest due to ventricular tachycardia or fibrillation, ICD implantation should be offered. Follow-up with lifevest during the acute episode and re-assessment of ICD requirement is another alternative option in patients with documented VT/VF episode.[73]

Immunmodulatory treatment
Antiviral Therapies

There are conflicting data about the use of antiviral agents in acute myocarditis. Pleconaril prevents the enterovirus from exposing its RNA, and in rhinoviruses Pleconaril prevents the virus from attaching itself to the host cell.[74] It is demonstrated that Pleconaril may have beneficial effects if it is administered in the early phase of the disease.[75] Acyclovir, gancyclovir and valgancyclovir can be used in Herpes virüs related viral myocarditis.[76] There are several drugs used to treat SARS-CoV-2 infection but all of them are administered experimentally and only some of them found to be effective by small population based studies.

Intravenous Immunglobulin

Immunglobulins have antiviral and immunmodulation effects. In children with acute myocarditis, high dose inravenous immunglobulin (IVIG) caused improvement in left ventricular functions and survival rates oneyear after administration.[77] Gullestad L et al., demonstrated that IVIG treatment elicits increase in LV ejection fraction in patients with symptomatic chronic heart failure patients. However; in another study IVIG had no beneficial effects on recent onset dilated cardiomyopathy due to biopsy proven viral myocarditis.[78]

IVIG use was reported in two cases of SARS-CoV-2 related myocarditis. IVIG was combined with steroid in one patient and combined with steroid and interferon-1 beta in another patient. Both of the patients recovered from the disaese and LV functions were improved after treatment.[79]

Immunoadsorption

The aim of Immunoadsorption is to remove antibodies damaging heart from blood. Immunoadsorption decreases myocardial inflammation and is associated with improvement in hemodynamic paramaters including cardiac stroke volume.[80] A randomized study with dilated cardiomyopathy patients have shown that immunoadsorption improves LV functions and decreased myocardial inflammation.[81]

Interferon-1 beta

Interferons (IFN)serve as a defense against most of viral infections. There are strong datase about use of interferons in rheumatic disease due to their immunomodulating

effects, there are limited datas about their administration in viral myocarditis. Efficacy of interferon beta-1a was assessed in patients with persistent adenovirus and enterovirus infection of myocardium and after 6 months of treatment; viral genomes were completely eliminated from myocardium and NYHA class was improved and heart failure related symptoms decreased significantly.[82] However, the beneficial effects of IFN-beta was observed to be less in Parvovirus and Herpes virüs associated myocarditis than enterovirus and adenovirus related myocarditis. Interferons are administered subcutaneously and have side effects including fatigue, influenza-like symptoms and inection site reactions. It should be noted that heart failure symptoms may worsen and LV functions may get worse between the 4th and 12th weeks of the treatment and it usually resolves 1-2 weeks later.[83] BICC study including 143 patients with viral myocarditis related dilated cardiomyopathy demonstrated that IFN-beta treatment is associated with significant reduction of viral genom in patients with entovirus infection while complete elimination could not be achieved in patients with Parvovirus B19 infection. It was also established that despite there were not significant change in LV parameters; only patient global assessment and NYHA functional class were improved.[84]

Immunsupressive treatment

Efficacy of prednisone was demonstrated in a randomised controlled trial in 1989. Steroid treatment resulted with higher LV ejection fraction and lower LV diameters in patients with dilated cardiomyopathy.[85] In another randomized trial; 3 months of treatment with corticosteroid and azathioprine combination improved LV parameters and heart failure symptoms in 41 patients with biopsy proven immune myocarditis.[86] TIMIC study included cases with virus negative inflammatory myocarditis and the study demonstrated that patients with azathioprine and prednisone treatment had better LVEF functions and functional capacity after 6 months follow up, while patients who underwent placebo arm had worse left ventricular functions after follow-up period.[87]

CURRENT DATA ABOUT THE MEDICAL TREATMENT OF SARS-COV-2 RELATED MYOCARDITIS

There are not any specific antiviral agent for SARS-CoV-2 but some drugs were shown to be effective in treatment of SARS-CoV-2 infection. Hydroxychloroquine, lopinavir/ritonavir, azithromycin, ivermectin, favipravir and remdesivir are some of the drugs that may have beneficial effects during SARS-CoV-2 infection. There are only case reports about SARS-CoV-2 related myocarditis. The cases reported with detailed treatment protocols are summarized in Table-1. The reported cases are severe cases with significant left ventricular dysfunction and cardiogenic shock. Most of the myocarditis cases usually have mild symptoms so probably the detected cases are just the tip of the iceberg.

Zeng JH et al. reported a 63 year old male patients with cardiogenic shock due to SARS-CoV-2 related myocarditis. His LVEF was 32% and the patient was transferred into intensive care unit due to fulminant myocarditis. Lopinavir/ritonavir, interferon alfa, steroid and IVIG were administered in addition to supportive care. Left ventriclar functions improved and patient recovered from myocarditis.[88] In another case report; a 37 year old male presented with fulminant myocarditis due to SARS-CoV-2 infection. Steroid and IVIG combination was administered in the early stage of the disease. Patient recovered from the disease one week later and discharged without any complications.

In the reported cases, methylprednisolone was used in 3 patients. The most common used antiviral agent was lopinavir/ritonavir and it was used in 3 patients. Hydroxychloroquine was used in two patients and IVIG was administered in two patients. IFN-beta was used only in one patient. All of the patients were recovered from myocarditis successfully (Table-1).[79,89]

Tocilizumab is an antibody against IL-6 receptor and is widely used in rheumatologic diseases. Tocilizumab was administered in some severe SARS-CoV-2 infection cases with ARDS, refractory shock, refractory fever or significantly high inflammatory markers and satisfactory resuls were obtained.[90]

TAKE HOME MESSAGES

- The obvious relationship between TnT levels and C-reactive protein and N-terminal pro-B-type natriuretic peptide levels indicates that myocardial injury is associated with the severity of inflammation and ventricular dysfunction.
- ACE inhibitors or ARBs should be administered in patients with wall motion abnormality or heart failure with reduced EF.
- Diuretics should be considered in patients with volume overload and torsemide should be preferred as first option.
- Beta blockers should be administered if patient had no contraindications such as bradycardia, acute decompansated heart failure, advanced AV block and carvedilol should be preferred. Metoprolol should be avoided.
- Non-steroidal antiinflammatory drugs and cardiac glycosides should be avoided.
- Physical activity should be restricted until the disease resolved.

Table 1: Treatment of Patients with SARS-CoV-2 Related Myocarditis

Patient No (Age/Gender) Country	Symptoms	Baseline ECG/Echo	Treatment	Outcome
Case 1 (37/Male) China	*Chest pain, dyspnea	* ST elevation in inferior leads * LV EDD: 58 mm * LV EF: 27% *Minimal pericardial effusion	*Methylprednizolone 200 mg/day (4 days) *IVIG 20 g/day (4 days) * Noradrenaline/milrinone * Torsemide * Piperacillin-tazobactam	*LV EF: 66% (1 week later) * Significant decrease in cardiac biomarkers
Case 2 (61/Male) China	*Productive cough, chest pain	* Sinus tachycardia * LV EDD: 61 mm * LV EF: 32%	* Lopinavir/ritonavir 2×500 mg * Interferon alfa * IVIG *Methylprednizolone * Piperacillin-tazobactam * ECMO * CRRT	*LV EF: 66% (15 days later) * Significant decrease in cardiac biomarkers and IL-6 level
Case 3 (53/Female) Italy	*Fever, cough, fatigue	*Low voltage in extremity leads * ST depression in V1 and aVR * LV EF: 40% * Moderate pericardial effusion * Mild diastolic dysfunction	* Dobutamine (4 days) * Canrenone 1×50 mg * Furosemide * Bisoprolol 1×2.5 mg *Methylprednizolone 1 mg/kg/day (3 days) *Hydroxychloroquine 2×200 mg * Lopinavir/ritonavir 2×500 mg * Aspirin 2×500 mg	*LV EF: 44% (6 days later) *Significant decrease in cardiac biomarkers and pericardial effusion
Case 4 (43/Female) Italy	*Fever, chest pain	* Low atrial rhythm * ST elevation in V1-2 and aR * U waves * LVE EF: 43% * İnferolateral wall hypokinesia	*Hydroxychloroquine 2×200 mg * Lopinavir/ritonavir 2×500 mg * CPAP (NIMV)	*LV EF: 65% * Significant decrease in cardiac biomarkers

- IVIG and interferon therapy are feasible treatment options with reasonable side effect profile.
- Patients requiring V-A ECMO support who incidentally test positive for COVID-19 but are not thought to be critically ill due to the virus should be considered for ECMO support in the usual fashion.

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