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ORIGINAL ARTICLE

Management of Immunosuppression Treatment in Autoimmune Liver Disease and Liver Transplantation Patients Infected with COVID-19

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Abstract

Introduction: It is known that viral infections progress more seriously in immunosuppressed patients than in the healthy population. In the literature, there is limited information on the course of COVID-19 infection in patients with autoimmune liver disease (AID) who receive immunosuppressive therapy, and in patients who have undergone liver transplantation. We present in detail the course of twelve patients, including six patients with AID and six patients with liver transplantation, who had COVID-19 infection and were followed up under immunosuppressive therapy.

Methods: Six AID and six liver transplant patients with COVID-19 infection were examined in detail from 58 AID and 72 liver transplant patients followed in the hepatology outpatient clinic of our hospital. Demographic data such as age and gender, underlying liver diseases, medical treatments received, and how medical treatment was affected during COVID-19 infection were examined in detail.

Results: The mean age of the twelve patients included in the study was 38.1±5.2 years, with 7 (58.3%) patients being male and 5 (46.7%) female. Two patients with cirrhosis-associated AID who are in remission under azathioprine monotherapy had their treatment dose reduced by half, while the others did not change. While the dose of immunosuppressant was reduced by half and methylprednisolone treatment was added in two of the transplant patients, no dose change was required in the other patient. All patients were discharged with full recovery.

Discussion and Conclusion: Interruption of immunosuppressive therapies is not appropriate because they prevent the activation of the underlying AID, prevent liver rejection in transplanted patients, as well as cytokine storm, which is the most important cause of mortality in COVID-19 disease. However, dose reduction can be made in selected cases.

Keywords: Autoimmune liver disease; immunosuppressive therapies; transplantation.

In the last months of 2019, a novel coronavirus, SARS-CoV-2, was identified as the cause of a group of pneumonia cases in Wuhan, a city in Hubei Province of China[1]. Coronavirus disease 2019 (COVID-19) manifests primarily as a lung infection with symptoms ranging from a mild upper respiratory tract infection to severe

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pneumonia, acute respiratory distress syndrome (ARDS), and death[2].

There is very limited information in the literature regarding the course of COVID-19 disease in autoimmune liver patients receiving immunosuppressive therapy and in patients with liver transplantation[3-5]. First of all, concerns have been raised for immunocompromised patients due to the possibility of decompensation of liver disease or the poor course of SARS-CoV-2 infection. AIH is a chronic autoimmune disease requiring immunosuppression in its maintenance, and cessation of immunosuppressive therapy is associated with an almost inevitable recurrence of the disease[6]. Similarly, immunosuppressive treatments in patients with liver transplantation both prevent rejection and the activation of underlying autoimmune diseases[5,7]. It is known that viral infections progress more seriously in an immunosuppressive host compared to a healthy population[6]. Therefore, there is no clarity yet on how to manage immunosuppression therapy during the SARS-CoV-2 pandemic. In our clinic, we have presented in detail the course of patients with COVID-19 that we followed up under immunosuppressive treatment, with the diagnosis of autoimmune disease of the liver and patients with liver transplantation.

Materials and Methods

Study Design

We included patients with COVID-19 disease who were followed up in our hospital's gastroenterology and hepatology outpatient clinic due to autoimmune liver disease and liver transplantation and received immunosuppressive therapy. Other liver diseases or autoimmune liver patients who did not receive immunosuppressive therapy were not included in the study. Our study was designed retrospectively. We investigated the course of patients with COVID-19 that we followed up under immunosuppressive treatment with the diagnosis of autoimmune disease of the liver and patients with liver transplantation. Demographic data of the patients, such as age and gender, were recorded. Liver disease and immunosuppressive drugs were questioned. Liver histopathology was recorded in non-transplant patients. Laboratory examinations were evaluated. The results of chest X-ray and thorax tomography were analyzed. The clinical course of the patient, the need for intensive care hospitalization, and how liver disease was affected were recorded.

Diagnosis of COVID-19 Disease

COVID-19 was confirmed in all patients either by a positive real-time polymerase chain reaction (RT-PCR) test of a nasopharyngeal or sputum sample or by a positive result on serological testing and compatible clinical presentation.

Ethical Statement

Ethical approval for this study was obtained from the Ethics Committee of our hospital (Approval no: 07/01/2021/2021-01). All procedures were in accordance with the ethical standards of our institution's human experiment committee and the Helsinki Declaration. Written informed consent forms were obtained from all participants in the study.

Statistical Analysis

The results of our study were analyzed with the program "The Statistical Package for the Social Sciences 19.0 (SPSS, Armonk, NY: IBM Corp.)". Data with continuous values were given as mean (±standard deviation), and categorical data as frequency and percentage (n,%).

Results

Among the 58 autoimmune liver patients and 72 liver transplant patients followed up in the gastroenterology outpatient clinic of our hospital, 3 with autoimmune hepatitis, 2 with autoimmune hepatitis and primary biliary cholangitis, 1 with autoimmune hepatitis and primary sclerosing cholangitis, and 6 liver transplantation patients, who had COVID-19 infection, were analyzed in detail. The mean age of the 12 patients included in the study was 38.1±5.2, with 7 (58.3%) being male and 5 (46.7%) female. Two patients had liver cirrhosis. The etiology of transplant patients was examined; three patients had liver cirrhosis due to hepatitis B infection, one patient had liver transplantation due to liver cirrhosis secondary to autoimmune hepatitis, one patient had liver transplantation due to liver cirrhosis secondary to primary biliary cholangitis, and one patient had liver transplantation due to liver cirrhosis secondary to primary sclerosing cholangitis.

Clinical, laboratory, and radiological features of patients with COVID-19 were analyzed in detail, and management of immunosuppressive treatment and outcome of patients was documented (Table 1).

Table 1. Clinical, Laboratory, Radiological Features, and Management of Immunosuppressive Treatment, Outcome of Patients with COVID-19

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Age	34	21	46	56
Sex	Male	Female	Male	Male
Etiology of Liver Disease	Compensated liver cirrhosis secondary to primary biliary cholangitis and autoimmune hepatitis	Autoimmune hepatitis	Liver transplantation due to liver cirrhosis caused by hepatitis B	Liver transplantation due to liver cirrhosis associated with primary sclerosing cholangitis
Medicine	Azathioprine 100 mg/day, Ursodeoxycholic acid 1000 mg/day	Azathioprine 50 mg/day	Tacrolimus 2 mg/day	Tacrolimus 2 mg/day, Everolimus 1 mg/day
Stage of Liver Disease	Fibrosis stage: 5, Hepatic activity index: 12	Fibrosis stage: 2, Hepatic activity index: 8	-	-
Leukocyte	13,200 /ml	9,500 /ml	9,600 /ml	14,200 /ml
Hb/Hct	14.7 g/dL, 47%	14.1 g/dL, 45%	14.5 g/dL, 46%	12.3 g/dL, 36%
Platelet	89,000 /ml	156,000 /ml	163,000 /ml	195,000 /ml
Creatinine	0.86 mg/dl	0.9 mg/dl	1.4 mg/dl	0.82 mg/dl
AST	19 U/L	79 U/L	26 U/L	42 U/L
ALT	22 U/L	86 U/L	18 U/L	65 U/L
ALP	65 U/L	163 U/L	56 U/L	128 U/L
GGT	22 U/L	120 U/L	25 U/L	89 U/L
CRP	25 mg/dl	19 mg/dl	56 mg/dl	92 mg/dl
Lung X-ray Radiography	Considering a new type of coronavirus infection	No findings compatible with pneumonia	Areas of consolidation present	Consolidation area in the left baseline
Thoracic CT	Ground-glass areas observed bilaterally in the middle areas and basals.	Normal	Bilateral diffuse ground-glass appearance	Diffuse ground-glass appearance bilaterally
Immunosuppressive Treatment Management	Azathioprine dose halved	Azathioprine continued at the same dose	Tacrolimus dose halved and methylprednisolone added	Tacrolimus and everolimus continued at the same dose
Stay in Intensive Care Unit	No	No	Yes	No
Result	Improvement	Improvement	Improvement	Improvement
Worsening of Liver Disease	No	No	No	No
	Patient 5	**Patient 6**	**Patient 7**	**Patient 8**
Age	39	25	41	58
Sex	Female	Male	Female	Female
Etiology of Live Disease	Compensated liver cirrhosis secondary to autoimmune hepatitis	Autoimmune hepatitis	Liver transplantation due to liver cirrhosis caused by hepatitis B	Liver transplantation due to liver cirrhosis associated with primary biliary cholangitis
Medicine	Azathioprine 100 mg/day	Azathioprine 50 mg/day	Tacrolimus 2 mg/day, Mycophenolate mofetil 500 mg/day	Tacrolimus 2 mg/day
Stage of Liver Disease	Fibrosis stage: 5, Hepatic activity index: 14	Fibrosis stage: 3, Hepatic activity index: 7	-	-
Leukocyte	6,200 /ml	8,500 /ml	8,600 /ml	13,200 /ml
Hb/Hct	13.7 g/dL, 47%	13.1 g/dL, 45%	13.5 g/dL, 46%	13.3 g/dL, 36%
Platelet	92,000 /ml	166,000 /ml	153,000 /ml	185,000 /ml
Creatinine	0.76 mg/dl	0.8 mg/dl	1.3 mg/dl	0.92 mg/dl
AST	29 U/L	89 U/L	36 U/L	32 U/L
ALT	25 U/L	76 U/L	28 U/L	55 U/L
ALP	75 U/L	173 U/L	50 U/L	118 U/L
GGT	32 U/L	131 U/L	29 U/L	80 U/L
CRP	26 mg/dl	29 mg/dl	59 mg/dl	42 mg/dl

Table 1. CONT.

Lung X-ray Radiography	Areas of consolidation present	No findings compatible with pneumonia	Areas of consolidation present	Areas of consolidation present
Thoracic CT	Ground-glass areas observed bilaterally in the middle areas	Normal	Bilateral diffuse ground-glass appearance	Ground-glass areas observed bilaterally in the baseline areas
Immunosuppressive Treatment Management	Azathioprine dose halved	Azathioprine continued at the same dose	Immunosuppressive dose halved and methylprednisolone added	Tacrolimus continued at the same dose
Stay in Intensive Care Unit	No	No	Yes	No
Result	Improvement	Improvement	Improvement	Improvement
Worsening of Liver Disease	No	No	No	No
	Patient 9	**Patient 10**	**Patient 11**	**Patient 12**
Age	24	31	36	47
Sex	Male	Female	Male	Male
Etiology of Liver Disease	Primary biliary cholangitis and autoimmune hepatitis	Autoimmune hepatitis and primary sclerosing cholangitis	Liver transplantation due to liver cirrhosis caused by hepatitis B	Liver transplantation due to liver cirrhosis associated with autoimmune hepatitis
Medicine	Azathioprine 100 mg/day, Ursodeoxycholic acid 1000 mg/day	Azathioprine 50 mg/day, Ursodeoxycholic acid 1000 mg/day	Tacrolimus 2 mg/day	Tacrolimus 2 mg/day, Mycophenolate mofetil 500 mg/day
Stage of Liver Disease	Fibrosis stage: 3, Hepatic activity index: 8	Fibrosis stage: 2, Hepatic activity index: 10	-	-
Leukocyte	11,300 /ml	8,600 /ml	8,200 /ml	9,200 /ml
Hb/Hct	13.8 g/dL, 47%	13.5 g/dL, 45%	12.9 g/dL, 46%	13.3 g/dL, 36%
Platelet	175,000 /ml	165,000 /ml	183,000 /ml	210,000 /ml
Creatinine	0.72 mg/dl	0.83 mg/dl	1.0 mg/dl	0.79 mg/dl
AST	21 U/L	26 U/L	35 U/L	33 U/L
ALT	26 U/L	36 U/L	25 U/L	45 U/L
ALP	66 U/L	63 U/L	63 U/L	98 U/L
GGT	28 U/L	30 U/L	28 U/L	68 U/L
CRP	35 mg/dl	19 mg/dl	16 mg/dl	42 mg/dl
Lung X-ray Radiography	Areas of consolidation present	No findings compatible with pneumonia	Areas of consolidation present	Consolidation area in the left baseline
Thoracic CT	Ground-glass areas observed bilaterally in the basals	Normal	Ground-glass areas observed bilaterally in the basals	Diffuse ground-glass appearance bilaterally
Immunosuppressive Treatment Management	Azathioprine continued at the same dose	Azathioprine continued at the same dose	Tacrolimus continued at the same dose	Tacrolimus and Mycophenolate mofetil continued at the same dose
Stay in Intensive Care Unit	No	No	No	No
Result	Improvement	Improvement	Improvement	Improvement
Worsening of Liver Disease	No	No	No	No

Hb: Hemoglobin; Hct: Hematocrit; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; GGT: Gamma-Glutamyl Transferase; CRP: C-Reactive Protein; CT: Computed Tomography.

Discussion

It remains unclear whether patients with chronic liver disease are more susceptible to SARS-CoV-2 infection. There is no known association between chronic liver disease and an increased risk of SARS-CoV-2 infection in the absence of immunosuppressive therapy[7]. The SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE-2) receptor to gain entry and damage the target organ. The presence

of ACE-2 receptors in the liver, bile, and liver epithelial cells may contribute to increased susceptibility to SARS-CoV-2 infection[8]. Studies have reported that COVID-19 has a worse prognosis in patients with chronic liver disease[9-11]. In a study evaluating 2,780 COVID-19 patients by Singh et al.,[10] it was observed that the mortality rate was three times higher in 250 chronic liver patients compared to non-cirrhotic patients. It has also been reported that there is a parallel between the increase in liver disease severity and mortality. Another study reported that mortality was significantly higher in patients with Child-Pugh B and C compared to those with Child-Pugh A[12].

The Centers for Disease Control and Prevention (CDC) state that patients with chronic liver disease or weakened immunity due to immunosuppressive therapy may have a higher risk of serious illness from COVID-19, although the supporting data is quite limited[11,13,14]. In their study, Pereira et al.[15] evaluated 90 patients with solid organ transplants and immunosuppressive therapy. It was observed that 27 (30%) patients had severe COVID-19, 41 (46%) patients had moderate COVID-19, and 22 (24%) patients had mild COVID-19. The analyses reported that the presence of comorbidities such as hypertension, diabetes, hyperlipidemia, obesity, and being over the age of 65 are risk factors for severe COVID-19[15]. However, it is not clear that immunosuppressive treatment worsens the course of the disease. Similarly, immunosuppressive therapy was not found to be associated with a worse course of the disease in transplant patients during the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks[16]. However, the overreaction of the host immune system, creating an intense inflammatory environment, can increase disease severity. In this regard, it has been reported that low-dose immunosuppressive therapy may improve the course of COVID-19[15-17].

In the data obtained from 67 liver units in Italy, 10 autoimmune hepatitis patients who were under immunosuppressive treatment and had COVID-19 were evaluated. The study included 6 non-cirrhotic patients and 4 cirrhotic patients (1 with decompensated liver cirrhosis). It was noted that all patients were symptomatic and showed virus antigen positivity in swab samples. Six patients were hospitalized, with five developing pneumonia, and three required continuous positive airway pressure (CPAP) support[3]. The researchers reported dose modifications in treatments: prednisone dosage was reduced for 3 patients, 1 patient voluntarily stopped prednisone, the prednisone dose was increased while decreasing the azathioprine dose in two patients, and the mycophenolate mofetil dose was reduced in one patient. The patient with decompensated liver cirrhosis was reported as a mortality case, while others recovered under treatment. Prednisone treatment was resumed for the patient who had voluntarily discontinued it due to a relapse[3]. In our cases, one patient in remission was on a low dose (50 mg/day) of azathioprine, which we continued at the same dose. For another patient with compensated liver cirrhosis and in remission under 100 mg/day azathioprine, we halved the immunosuppressive dose. Both cases recovered smoothly during follow-up. Post-COVID-19, we reinstated the original immunosuppressive treatment dose.

In conclusion, there is still no clear data regarding the management of COVID-19 in patients with autoimmune liver diseases and liver transplant recipients. However, analysis of our own cases and reported cases suggests that while interruption of immunosuppressive therapies for autoimmune diseases is not advisable, as they prevent the activation of underlying disease and liver rejection in transplant patients, as well as mitigate cytokine storm - a major cause of mortality in COVID-19 - dose reduction may be considered in selected cases.

Ethics Committee Approval: Van Education and Research Hospital Ethics Committee (Approval no: 07/01/2021/2021-01).

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Conflict of Interest: None declared.

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