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Coronavirus Disease 2019 (COVID-19) in autoimmune hepatitis: a lesson from immunosuppressed patients

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Abstract

Background & Aims. Chronic immunosuppression is associated with increased and more severe viral infections. However, little is known about the association between immunosuppression and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Our aim was to describe the clinical course of immunosuppressed autoimmune hepatitis (AIH) patients during coronavirus disease 2019 (COVID-19) infection in Italy.

Methods. Our study is a case series of AIH patients treated with immunosuppression, who tested positive for SARS-CoV-2 in March 2020 during outbreak of COVID-19.

Results: Ten patients from six different hospitals in Italy were diagnosed with COVID-19 during the outbreak of SARS-CoV-2 in March 2020. Seven subjects were female (70%) and age ranged from 27 to 73 years. Before the onset of SARS-CoV-2 infection, all patients were taking immunosuppressive therapy for AIH, and eight of them were on biochemical remission. Two other patients had recent acute onset of their AIH, and were consequently started high-dose steroids, as per induction protocol. All patients had a respiratory syndrome and had a positive nasal swab for SARS-CoV-2. Five patients developed a CT-confirmed COVID-19 pneumonia. Six subjects received a combination of antiretroviral and antimalarial drugs. In seven patients the dosage of immunosuppressive medication was changed. Liver enzymes were repeated during SARS-CoV-2 infection in all hospitalized cases; they remained within the normal range in all cases, and improved in the two acute cases treated with high-dose steroids. The clinical outcome was comparable to the reported cases occurring in non-immunosuppressed subjects.

Conclusion: Patients under immunosuppressive therapy for AIH developing COVID-19 show a disease course presumptively similar to that reported in non-immunosuppressed population. These data might help medical decision when dealing with SARS-CoV-2 infection in immunocompromised patients.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pandemic infection causing coronavirus disease 2019 (COVID-19), and Italy is one of the mostly affected countries worldwide(1). The impact of COVID-19 in patients with autoimmune liver disease treated with immunosuppressive therapy have not been described so far. Mainly, concerns have been raised for immunosuppressed patients, particularly those with autoimmune hepatitis (AIH), due to the possibility of decompensation of liver disease, or to an unfavorable course of SARS-CoV-2

infection. AIH is a rare liver disease and a prototypical example of chronic autoimmune condition requiring maintenance immunosuppression(2). Stopping immunosuppression is associated with almost inevitable relapse of the disease(3). Viral infections in immunocompromised host are more frequent than in the general population, and have the ability to cause severe disease at much higher rates than in the healthy population(4,5). Nonetheless, data from previous outbreaks of Coronaviruses infections, like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), did not report a higher risk of morbidity and mortality related to immunosuppression(6). Therefore, there is uncertainty on how to manage immunosuppression therapy during SARS-CoV-2 pandemic.

This report describes the clinical course of ten AIH patients who developed COVID-19 in Italy. Patients provided informed consent for the inclusion in this study, and the diagnostic procedures were conducted in accordance with institutional guidelines.

Case series

We contacted 67 large Italian liver units (24 in Lombardy) during the outbreak of SARS-CoV-2 asking about cases of COVID-19 occurred in patients with AIH followed-up at these centers.

Ten patients with AIH from seven different hospitals in Italy, mainly located in Lombardy Region, were diagnosed with COVID-19 during the outbreak of SARS-CoV-2 in March 2020 (**Table**). Seven subjects were female (70%) and age ranged from 27 to 73 years. Cirrhosis was present in four cases (40%) and patient 6 had decompensated cirrhosis (Child-Pugh B), with history of previous episodes of ascites and hepatic encephalopathy.

Before the onset of COVID-19, all patients were taking immunosuppressive therapy with different dosages: all but one (patient 8) were on steroids (prednisone), and four (40%) were on azathioprine; patient 1 was on triple immunosuppressive regimen due to difficult-to-treat AIH. The immunosuppression regimen was stable in eight patients who were on biochemical remission at recent evaluation. Two other patients (patient 2 and 4) had an acute onset of AIH and were under high-dose steroids, as per induction protocol, at the time of SARS-CoV-2 infection.

All cases were symptomatic for respiratory syndrome and positive for SARS-CoV-2 at nasal swab; four cases were managed at home under compulsory quarantine. Among those managed at

home, one patient was afebrile, had persistent cough and headache; the others were febrile and had cough as main symptom. Among the six hospitalized subjects, five developed a CT-confirmed COVID-19 pneumonia. Three patients were treated with continuous positive airway pressure support for hypoxemic respiratory failure.

All subjects received a combination of an antiretroviral drug (either lopinavir/ritonavir or darunavir/cobicistat) with an antimalarial medication (either hydroxychloroquine or chloroquine); two cases were also treated with azithromicine. Empirical therapies for SARS-CoV-2 infection were in line with recommendations given by the infectious disease service of each hospital.

In seven patients the dosage of immunosuppressive therapy was changed. Prednisone regimens were heterogeneously managed: in three cases doses were reduced, while Patient 9 self-stopped it. Patient 2 and 4 were given high dose corticosteroids to induce remission and tapering dosage thereafter. In two cases only prednisone regimen was increased. Azathioprine was stopped in patient 1 and 2; in patient 1 prednisone was reduced from 10 to 7.5 mg/day, while tacrolimus was maintained at the same dose.

Liver enzymes were repeated during SARS-CoV-2 infection in all hospitalized cases, and remained within the normal range in all cases except for patient 2 and 4, in whom liver function tests dramatically improved. In four hospitalized cases data about lymphocyte count were available; all patients experienced acute lymphopenia (severe in two subjects), that was not present before admission and fully reverted after COVID-19.

At the time of submission nine patients are still alive, of whom nine are asymptomatic, and patient 6 has died. Patient 9, who had previously self-stopped immunosuppression with steroids, has experienced a relapse of AIH and is now treated with prednisone 50 mg/day.

Discussion

We report here the first ten cases of COVID-19 occurred in patients with AIH under immunosuppressive treatment. With the limitation of the short follow-up and the lack of a control group of non-AIH patients, we do report a somehow unremarkable COVID-19 disease course despite ongoing immunosuppression. Remarkably, one patient went through COVID-19 without developing pneumonia despite the combination of compensated cirrhosis and acute AIH, with consequent need for high-dose induction with steroids. The death event occurred in the frailest

patient included in the cohort (patient 6), who had already decompensated cirrhosis, which is associated with significant morbidity and mortality(7). Moreover, we believe that pre-emptive strategies of reduction of immunosuppression during COVID-19 can be potentially harmful, as suggested by the disease course of patient 9 that self-stopped steroid treatment and relapsed after SARS-CoV-2 infection. There is a growing evidence that part of the morbidity of COVID-19 is due to the hyperinflammation and cytokine storm(8), as supported by data from China which showed that high levels of IL-6 are associated with increased mortality(9) and the supposed beneficial effects of immunomodulators (Tocilizumab and other IL-6 blockers(10), Baricitinib(11)). Recently, a systems pharmacology-based network medicine platform identified mercaptopurine as one of the potential drugs to treat COVID-19(12). Mercaptopurine, also known as 6-mercaptopurine, is a metabolite of Azathioprine, and together with Azathioprine belongs to the group of thiopurines, the most commonly used drugs for AIH maintenance. Thus, one could speculate that empirical strategies of reduction of immunosuppression in patients affected by chronic autoimmune diseases might be even harmful if immunosuppression might at least counterbalance COVID-19-driven hyperinflammation.

One of the known side effects of thiopurines is lymphopenia, which is often mild-to-moderate and considered a parameter of effective immunosuppression(13). Yet, lymphopenia is known to predispose to viral infections, and thiopurines have been linked with increased incidence of opportunistic viral infections in patients with inflammatory bowel disease(4). Data from Wuhan experience have clearly shown that most patients with SARS-CoV-2 infection have lymphopenia(14), and our data are in line with Chinese findings. The lack of a control group of non-AIH patients and the nature of this manuscript (case series) do not allow us to draw conclusions regarding the possible association between chronic treatment with thiopurines and the risk of developing COVID-19. Whether it would be sensible to stop thiopurines and increase steroids in patients with COVID-19 treated with immunosuppression is difficult to be ascertained and more evidence is needed. One should consider that it is highly likely that the immunosuppressive effect of thiopurines would not immediately cease after drug withdrawal, thanks to their mechanism of action(15), while this is probably not true for steroids, as suggested by the early relapse occurred in case number 9. Moreover, there is a well-established literature showing that patients with AIH in stable control of their disease are at high risk of relapse when suddenly reduce/stop their immunosuppression, so that empirical change of immunosuppressive medications should be considered with caution(3,16) before more evidence is available.

The main limitations of this study are the small sample size and the short follow-up, that prevent us to infer whether treated AIH patients have a specific clinical phenotype: to answer this research question we would have need a larger sample size and longer observation. In addition, the approach toward immunosuppression was too heterogenous to draw solid conclusions, especially regarding the beneficial or detrimental role of steroids during COVID-19. Finally, this study does not allow to understand whether treated AIH patients are more or less prone to develop COVID-19, lacking a non-AIH control group. However, since COVID-19 is a rapidly evolving epidemic which is affecting countries with a different time fashion, we believe our data are timely and could be of value for clinicians.

COVID-19 in patients with AIH treated with immunosuppression seems to have a disease course presumptively similar to general population. We believe that empirical reduction of immunosuppression in patients with AIH (and, by extension, other autoimmune conditions) during COVID-19 might be harmful, since it could expose individuals to a higher risk of relapse of the disease(3). Moreover, for most immunosuppressive drugs the immunosuppressant effect would take weeks before disappearing. Up to now, a case-by-case approach is warranted, adopting clinical judgement until more data are collected and can guide the management of these challenging cases.

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ID	1	2	3	4	5	6	7	8	9	10
Age, y	27	55	45	55	53	68	55	65	68	73
Sex	F	M	F	M	F	F	F	M	F	F
Cirrhosis	yes	no	no	yes	yes	yes	no	no	no	no
Date of previous labs	17/02/2020	14/02/2020	23/01/2020	09/03/2020	26/09/2019	04/03/2020	01/02/2020	15/03/2020	28/02/2020	20/02/202
AST, U/L	21	37	22	317	34	N/A	37	19	50	27
ALT, U/L	17,4	52	24	497	36	21	19	14	30	16
T Bil, mg/dl	0,4	1,0	1,0	2,6	1,0	0,9	1,6	0,6	1,0	N/A
Alb, g/dl	3,9	3,5	4,2	3,0	3,7	N/A	4,3	N/A	N/A	3,9
PLT, $\times 10^3/\mu L$	146	255	314	124	177	93	159	N/A	N/A	215
Lymph, x $10^9/L$	N/A	N/A	2,6	2,5	2,8	N/A	N/A	2,1	N/A	N/A
IgG, g/l	14,0	10,0	11,6	33,7	7,8	N/A	N/A	N/A	N/A	N/A
P pre	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Dose (mg)	10	40	10	60	10	5	5		25	20
AZA pre	Yes	Yes	No	No	No	No	Yes	No	No	Yes
Dose (mg)	50	50					100			75
Other drugs for AIH	Tac		No	No	No	No	No	MMF	No	No
Dose	1 mg q12h							1500 mg/day		
Clinical course										
Symptoms onset	07/03/2020	06/03/2020	05/03/2020	17/03/2020	01/03/2020	15/03/2020	18/03/2020	11/03/2020	01/03/2020	27/02/202

Clinical features	Cough, Headache	Fever	Fever, Cough	Fever, Cough	Cough, Fever, Diarrhoea	Cough, Fever	Cough, Fever	Fever, Cough	Fever, Ageusia	Fever, Cou
Swab positive for SARS-CoV-2?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Managed at home or at the hospital?	Home	Hospital	Hospital	Hospital	Hospital	Hospital	Home	Hospital	Home	Home
Pneumonia?	N/A	Yes	Yes	Yes	No	Yes	N/A	Yes	N/A	N/A
Respiratory failure?	No	No	Yes	No	No	Yes	No	Yes	No	No
Any change of drugs for AIH?	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
If yes, which drug was changed?	P, Aza	P, Aza		P	P	P		MMF	P	
Dose change	P ↓ 7.5 mg/day, Aza X	P ↓ 30 mg/day, Aza X		P ↓ 40 mg/day	P ↑	P ↑ 25 mg/day		MMF ↓ 1000 mg/day	Self-stopped	
Date of change	15/03/2020	07/03/2020		20/03/2020	10/03/2020	26/03/2020		26/03/20	02/03/2020	
Date of return to previous dose	not yet	not yet		not yet	23/03/2020	not yet		not yet	16/05/2020**	
Drugs for Covid-19	/	H, L/R, Azi	H, L/R	H, D/C	C, L/R	H, L/R	/	H, L/R, Azi	/	/

Repeated liver enzymes during COVID-19?	No*	Yes	Yes	Yes	Yes	Yes	No*	Yes	No*	No*
AST, U/L		39	23	82	98	34		22		
ALT, U/L		38	17	101	46	31		11		
T Bil, mg/dl		1,5	0,9	3,2	1,0	0,8		0,7		
Alb, g/dl		3,5	3,6	2,6	3,4	N/A		N/A		
Lymph, x 10^9/L		N/A	0,7	0,6	0,3	N/A		0,5		
Follow-up labs	27/04/2020	19/05/2020	20/03/2020	26/03/2020	18/03/2020	No	No	01/04/2020	15/05/2020	12/05/202
AST, U/L	25	39	30	66	36			27	600	11
ALT, U/L	34	39	30	89	27			14	599	17
T Bil, mg/dl	0,6	0,7	N/A	2,2	1			0,4	2,4	
Alb, g/dl		37	N/A	N/A	34					39
Lymph, x 10^9/L	1,6	3,5	1,5	3,9	1,6			1,0	1,4	
Current status (at 21/05/2020)	A	A	A	A	A	Exitus on 1st April 2020	A	A	A	A

Table. Clinical course and laboratory results

Abbreviations

Y, years; F, female; M, male; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T Bil, total bilirubin; PLT, platelets; IgG, Immunoglobulin G; Lymph, lymphocytes; P, prednisone; Aza, azathioprine; N/A, not applicable; AIH, autoimmune hepatitis; MMF,

mycophenolate; TAC, tacrolimus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; H, hydrochloroquine; L/R, lopinavir/ritonavir; Azi, azithromycin; D/C, darunavir/cobicistat; C, chloroquine; A, asymptomatic.

SI conversion factors: To convert platelet count to $\times 10^9$ per liter, multiply by 1.

*Blood exams not repeated due to restrictions related to compulsory quarantine at home.

**Restarted with Prednisone 50 mg for the treatment of the relapse of AIH.