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 patients with immunosuppressed autoimmune hepatitis (AIH) during coronavirus disease 2019 (COVID-19) infection in Italy. Our study is a case series of patients with AIH treated with immunosuppression, who tested positive for SARS-CoV-2 in March 2020 during the outbreak of COVID-19. Ten patients from seven 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 consequently started high-dose steroids, as per induction protocol. All patients had a respiratory syndrome and a positive nasal swab for SARS-CoV-2. Five patients developed a computed tomography–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 the non-immunosuppressed population. These data might aid in medical decisions when dealing with SARS-CoV-2 infection in immunocompromised patients. (Hepatology Communications 2020;4:1257-1262).
example of chronic autoimmune condition requiring maintenance immunosuppression. (2) Stopping immunosuppression is associated with almost inevitable relapse of the disease. (3) Viral infections in an 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 Coronavirus infections, like severe acute respiratory syndrome and Middle East respiratory syndrome, 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 the SARS-CoV-2 pandemic.

This report describes the clinical course of ten patients with AIH 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 that occurred in patients with AIH followed up at these centers.

Ten patients with AIH from seven different hospitals in Italy, located primarily in the Lombardy region, were diagnosed with COVID-19 during the outbreak of SARS-CoV-2 in March 2020 (Table 1). 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 (patients 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 and had persistent cough and headache; the others were febrile and had cough as main symptom. Among the six hospitalized subjects, five developed a computed tomography–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

ARTICLE INFORMATION:

From the 1Division of Gastroenterology and Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; 2European Reference Network on Hepatological Diseases, San Gerardo Hospital, Monza, Italy; 3Department of Translational Medicine, Università del Piemonte Orientale UPO, Novara, Italy; 4Division of Internal Medicine, AOUMaggiore della Carità, Novara, Italy; 5Gastroenterology Unit, Cardinal Massaia Hospital, Asti, Italy; 6Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; 7European Reference Network on Hepatological Diseases, Gastroenterology Unit, Azienda Ospedaliera Universitaria Padova, Padova, Italy; 8IRCCS Negrar, Verona, Italy; 9Internal Medicine Unit, ASST Lecco, Lecco, Italy; 10Liver Unit, Evangelico Betania Hospital, Napoli, Italy; 11Gastroenterology, Hepatology and Liver Transplantation Unit, Department of Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Pietro Invernizzi, M.D., Ph.D.
Division of Gastroenterology and Center for Autoimmune Liver Diseases
Department of Medicine and Surgery
University of Milano-Bicocca
Via Cadore 48
20900 Monza, Italy
E-mail: pietro.invernizzi@unimib.it
Tel.: +39 039 233 2187
### TABLE 1. CLINICAL COURSE AND LABORATORY RESULTS

| Patient ID | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|------------|----|----|----|----|----|----|----|----|----|----|
| Age, years | 27 | 55 | 45 | 55 | 53 | 68 | 55 | 65 | 68 | 73 |
| Sex        | F  | M  | F  | F  | F  | F  | F  | M  | F  | F  |
| Cirrhosis  | Yes| No | No | Yes| Yes| Yes| Yes| No | No | No |
| Date of previous labs | Feb 17, 2020 | Feb 14, 2020 | Jan 23, 2020 | Mar 9, 2020 | Mar 26, 2019 | Mar 4, 2020 | Feb 1, 2020 | Mar 15, 2020 | Feb 28, 2020 | Feb 20, 2020 |
| 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/μL | 146| 255| 314| 124| 177| 93 | 159| N/A| N/A| 215|
| Lymph, \times 10^9/L| N/A| N/A| 2.6| 2.5| 2.8| N/A| N/A| N/A| 2.1| 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| No | No | No | No | Yes| No| No| Yes |
| Dose, mg    | 50 | 50 | No| No | No | No| No| 100| 75 |
| Other drugs for AIH | Tac| No| No| No| No| No| No| MMF| No| No |
| Dose        | 1 mg every 12 hours | | | | | | | | 1,500 mg/day |
| Clinical course symptoms onset | Mar 7, 2020 | Mar 6, 2020 | Mar 5, 2020 | Mar 17, 2020 | Mar 1, 2020 | Mar 15, 2020 | Mar 18, 2020 | Mar 11, 2020 | Mar 1, 2020 | Feb 27, 2020 |
| Clinical features | Cough, headache | Fever, cough | Fever, cough | Cough, fever, diarrhea | Cough, fever, diarrhea | Cough, fever | Cough, fever | Fever, cough | Fever, ageusia | Fever, cough |
| Swab positive for SARS-CoV-2 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Managed at home or at hospital | Home | 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 |
| Any change of drugs for AIH | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| If yes, which drug was changed? | P, Aza | 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 ↑ 25 mg/day | MMF ↓ 1,000 mg/day | Self-stopped |
| Date of change | Mar 15, 2020 | Mar 7, 2020 | Mar 20, 2020 | Mar 10, 2020 | Mar 26, 2020 | Mar 26, 2020 | Feb 3, 2020 |
| Date of return to previous dose | Not yet | Not yet | Not yet | Mar 23, 2020 | Not yet | Not yet | May 16, 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 | / | / |
### Table 1. Continued

| Patient ID | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|------------|----|----|----|----|----|----|----|----|----|----|
| Repeated liver enzymes during COVID-19 | No* | Yes | Yes | Yes | Yes | No* | Yes | No* | No* | No* |
| AST, U/L | 39 | 23 | 82 | 98 | 34 | 22 | 22 | 22 | 22 | 22 |
| ALT, U/L | 38 | 17 | 101 | 46 | 31 | 11 | 11 | 11 | 11 | 11 |
| T Bil, mg/dL | 1.5 | 0.9 | 3.2 | 1.0 | 0.8 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 |
| Alb, g/dL | 3.5 | 3.6 | 2.6 | 3.4 | N/A | N/A | N/A | N/A | N/A | N/A |
| Lymph, x10^9/L | N/A | 0.7 | 0.6 | 0.3 | N/A | N/A | N/A | N/A | N/A | N/A |
| Follow-up labs | Apr 27, 2020 | May 19, 2020 | Mar 20, 2020 | Mar 26, 2020 | Mar 18, 2020 | No | No | Apr 1, 2020 | May 15, 2020 | May 12, 2020 |
| 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 | 39 |
| Alb, g/dL | 37 | N/A | N/A | 34 | 1.0 | 1.4 | 39 |
| Lymph, x10^9/L | 1.6 | 3.5 | 1.5 | 3.9 | 1.6 | 1.0 | 1.4 | 39 |
| Current status (as of May 21, 2020) | A | A | A | A | A | Exitus on Apr 1, 2020 | A | A | A | A |

SI conversion factors: to convert platelet count to ×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.

Abbreviations: A, asymptomatic; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Aza, azathioprine; Azi, azithromycin; C, chloroquine; D/C, darunavir/cobicistat; F, female; H, hydrochloroquine; IgG, Immunoglobulin G; L/R, lopinavir/ritonavir; Lymph, lymphocytes; M, male; MMF, mycophenolate; N/A, not applicable; P, prednisone; PLT, platelets; T Bil, total bilirubin; TAC, tacrolimus; Y, years.
heterogeneously managed: in three cases doses were reduced, while patient 9 self-stopped it. Patients 2 and 4 were given high-dose corticosteroids to induce remission and tapering the dosage thereafter. In two cases, only the prednisone regimen was increased. Azathioprine was stopped in patients 1 and 2; in patient 1, prednisone was reduced from 10 mg/day 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 patients 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), which was not present before admission and fully reverted after COVID-19.

At the time of submission, nine patients are still alive and 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 being 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 patients without AIH, 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 already had decompensated cirrhosis, which is associated with significant morbidity and mortality. 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, who self-stopped steroid treatment and relapsed after SARS-CoV-2 infection. There is growing evidence that part of the morbidity of COVID-19 is due to the hyperinflammation and cytokine storm, as supported by data from China, which showed that high levels of IL-6 are associated with increased mortality and the supposed beneficial effects of immunomodulators (tocilizumab and other IL-6 blockers) such as baricitinib. Recently, a systems pharmacology–based network medicine platform identified mercaptopurine as one of the potential drugs to treat COVID-19. 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. 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. Data from the Wuhan experience have clearly shown that most patients with SARS-CoV-2 infection have lymphopenia, and our data are in line with Chinese findings. The lack of a control group of patients without AIH 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, while this is probably not true for steroids, as suggested by the early relapse occurred in case number 9. Moreover, there is well-established literature showing that patients with AIH in stable control of their disease are at high risk of relapse when they suddenly reduce/stop their immunosuppression; therefore, empirical change of immunosuppressive medications should be considered with caution before more evidence is available.
The main limitations of this study are the small sample size and the short follow-up, which prevent us to infer whether patients with treated AIH have a specific clinical phenotype. To answer this research question, we would 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 us to understand whether patients with treated AIH are more or less prone to develop COVID-19, lacking a non-AIH control group. However, because COVID-19 is a rapidly evolving epidemic that is affecting countries with different time frames, we believe our data are timely and could be of value for clinicians.

COVID-19 in patients with AIH treated with immunosuppression appears to have a disease course presumptively similar to the 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, as it could expose individuals to a higher risk of relapse of the disease. Moreover, for most immunosuppressive drugs, the immunosuppressant effect would take weeks before disappearing. Up until 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.

REFERENCES

1) Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020 Mar 17. https://doi.org/10.1001/jama.2020.4344. [Epub ahead of print]
2) Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006;354:54-66.
3) Van Gerven NMF, Verwer BJ, Witte BI, Van Hoek B, Coenraad MJ, Van Erpecum KJ, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol 2013;58:141-147.
4) Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. Gastroenterology 2018;155:337-346.e10.
5) Kaltas A, Sepkowitz K. Community acquired respiratory and gastrointestinal viral infections: challenges in the immunocompromised host. Curr Opin Infect Dis 2012;25:423-430.
6) Hui DS, Azhar EI, Kim Y-J, Memish ZA, Oh M, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect Dis 2018;18:e217-e227.
7) European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406-460. https://doi.org/10.1016/j.jhep.2018.03.024.
8) Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;6736:19-20.
9) Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-848.
10) Ge Y, Tian T, Huang S, Wan F, Li J, Li S, et al. A data-driven drug repositioning framework discovered a potential therapeutic agent targeting COVID-19. bioRxiv 2020. https://doi.org/10.1101/2020.03.11.986836.
11) Strebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020. https://doi.org/10.1016/S1473-3099(20)30132-8.
12) Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov 2020;6:14.
13) Vogelin M, Biedermann L, Frei P, Vavrícka SR, Scharl S, Zeitz J, et al. The impact of azathioprine-associated lymphopenia on the onset of opportunistic infections in patients with inflammatory bowel disease. PLoS One 2016;11:e0155218.
14) Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMo a2002032.
15) Bayoumy AB, Sinseik M, Seinen ML, Mulder CJJ, Ansari A, Peters CJ, et al. The continuous rediscovery and the benefit–risk ratio of thioguanine, a comprehensive review. Expert OpinDrug Metab Toxicol 2020;16:111-123.
16) Montano-loza AJ, Carpenter HA, Czaa AJ. Consequences of treatment withdrawal in type 1 autoimmune hepatitis. Liver Int 2007;27:507-515.