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ORIGINAL ARTICLE

Effects of immunosuppressive drugs on COVID-19 severity in patients with autoimmune hepatitis

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Abstract

Background: We investigated associations between baseline use of immunosuppressive drugs and severity of Coronavirus Disease 2019 (COVID-19) in autoimmune hepatitis (AIH).

Patients and methods: Data of AIH patients with laboratory confirmed COVID-19 were retrospectively collected from 15 countries. The outcomes of AIH patients who were on immunosuppression at the time of COVID-19 were compared to patients who were not on AIH medication. The clinical courses of COVID-19 were classified as (i)-no hospitalization, (ii)-hospitalization without oxygen supplementation, (iii)-hospitalization with oxygen supplementation by nasal cannula or mask, (iv)-intensive care unit (ICU) admission with non-invasive mechanical ventilation, (v)-ICU admission with invasive mechanical ventilation or (vi)-death and analysed using ordinal logistic regression.

Results: We included 254 AIH patients (79.5%, female) with a median age of 50 (range, 17-85) years. At the onset of COVID-19, 234 patients (92.1%) were on treatment with glucocorticoids (n = 156), thiopurines (n = 151), mycophenolate mofetil (n = 22) or tacrolimus (n = 16), alone or in combinations. Overall, 94 (37%) patients were hospitalized and 18 (7.1%) patients died. Use of systemic glucocorticoids (adjusted odds ratio [aOR] 4.73, 95% CI 1.12-25.89) and thiopurines (aOR 4.78, 95% CI 1.33-23.50) for AIH was associated with worse COVID-19 severity, after adjusting for age-sex, comorbidities and presence of cirrhosis. Baseline treatment with mycophenolate mofetil (aOR 3.56, 95% CI 0.76-20.56) and tacrolimus (aOR 4.09, 95% CI 0.69-27.00) were also associated with more severe COVID-19 courses in a smaller subset of treated patients.

Conclusion: Baseline treatment with systemic glucocorticoids or thiopurines prior to the onset of COVID-19 was significantly associated with COVID-19 severity in patients with AIH.

KEYWORDS
autoimmunity, azathioprine, budesonide, liver transplantation, mercaptopurine, SARS-CoV-2

1 | INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has rapidly spread worldwide causing an ongoing pandemic since December 2019. The majority of COVID-19 cases have mild symptoms while individuals with older age and co-morbid conditions such as cardiovascular diseases, chronic lung/kidney diseases and diabetes mellitus are at increased risk of severe COVID-19 outcomes.[1,2] The liver is also commonly affected by COVID-19[3,4] and patients with underlying chronic liver diseases have high rates of hospitalization and death.

Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease treated by immunosuppressive therapy. Approximately, 80% of AIH patients respond to standard therapy (glucocorticoids and/or thiopurines). Mycophenolate mofetil (MMF) and tacrolimus are alternative immunosuppressive drugs for patients who do not respond or are intolerant to standard therapy.[5,6] Some studies have suggested that baseline therapy with glucocorticoids and thiopurines is associated with an increased risk of severe COVID-19 for patients with inflammatory bowel diseases (IBD) or rheumatic disorders.[7-9] On the other hand, baseline use of tacrolimus was associated with a better

COVID-19 outcome while MMF was linked to severe COVID-19 in liver transplant recipients.[10,11]

Data regarding the clinical presentation and outcome of COVID-19 in AIH patients are limited to two international registry studies, and a retrospective case study.[12-14] These studies suggested that the continuation of immunosuppressive therapy during COVID-19 infection was not associated with adverse outcomes in AIH.

In our previous study,[13] we described factors that were associated with severe COVID-19 outcome in patients with AIH. Because of sample size limitations, we could not fully evaluate any potential impact of baseline AIH medications on COVID-19 course. We have extended our data and now aim to explore the impact of AIH medications, including glucocorticoids, thiopurines, MMF and tacrolimus, on the risk of worse COVID-19 severity.

Lay summary

In this large cohort of patients with AIH, baseline treatment with glucocorticoids and thiopurines prior to the onset of COVID-19 was associated with worse COVID-19 severity. Our findings provide data to clinicians for management of AIH patients with COVID-19 and highlight the importance of preventive public health measures for these patients during the COVID-19 pandemic.

2 | MATERIALS AND METHODS

2.1 | Study design

We retrospectively evaluated data of AIH patients who were diagnosed with COVID-19 between March 11, 2020, and May 15, 2021, from 15 countries. All participants independently identified patients and collected data from electronic health records and patient charts using the same case report form. Only AIH patients who were older than 16 years at the time of COVID-19 with a diagnosis confirmed by a PCR-based test were included in the study. The diagnosis of AIH or AIH-variant with primary biliary cholangitis or primary sclerosing cholangitis and the treatment responses were ascertained according to international guidelines.[5,6] Complete biochemical response was defined as normalization of serum aminotransferases and immunoglobulin G levels. A lack of normalization of aminotransferases during immunosuppressive therapy was defined as non-response.[5]

2.2 | Data collection

We collected general information about patients, types and doses of immunosuppression, AIH response status at last follow-up before COVID-19 and the presence of cirrhosis. Clinical symptoms at COVID-19 diagnosis, co-morbid conditions, modifications in the dose or type of immunosuppressive medications during COVID-19, highest care level, hospitalization time, specific COVID-19 therapies and patient outcomes were also recorded.

2.3 | Exposure

Patients were classified into mutually exclusive exposure categories according to their baseline AIH treatment in a hierarchical manner. These were no treatment <glucocorticoids <thiopurines <MMF and tacrolimus. The highest-ranking treatment for each patient according to this hierarchy was considered the primary treatment and the use of combination treatment was indicated by a binary variable when the primary treatment was used in combination with another immunosuppressive drug or glucocorticoids.

2.4 | Confounders

Potential confounders for the association between a type of treatment and COVID-19 outcomes were demographic characteristics and comorbidities (Table 1). The presence of cirrhosis was included as a separate variable since it is strongly associated with worse outcomes of COVID-19 in patients with AIH.[4,12,13]

2.5 | Outcomes

We obtained complete COVID-19 disease course data for all patients who ultimately recovered from or died of the disease. The severity of COVID-19 was classified using a 6-level ordinal scale indicating the worst clinical state throughout the disease course[15]: (i) no hospitalization, (ii) hospitalization without oxygen supplementation, (iii) hospitalization requiring oxygen supplementation by nasal cannula or mask, (iv) intensive care unit (ICU) admission requiring non-invasive mechanical ventilation, (v) ICU admission requiring invasive mechanical ventilation and, (vi) death. This ordinal COVID-19 outcome spectrum was modified and adapted from the WHO clinical progression scale.[15] The Harran University Hospital of Şanlıurfa was the coordinating centre and local ethics review boards of centres providing patient data approved the study.

2.6 | Statistical analysis

Participant characteristics were illustrated using appropriate descriptive statistics. The primary analysis was performed using an ordinal logistic regression model. Exponentiated coefficients from this model for the treatment term indicate odds ratios of attaining a worse outcome. We reported crude odds ratios, as well as odds ratios after adjusting for age, sex, and odds ratios after adjusting also for the presence of cirrhosis, the number of comorbidities at baseline and presence of additional immunosuppressive or glucocorticoids alongside the primary

treatment. All analyses were performed using the open-source R software v. 4.0.3 (R foundation for statistical computing, Vienna, Austria) running under the IDE, R Studio v. 1.4.1 using the MASS package.

3 | RESULTS

3.1 | General characteristics of the study population

Data from 264 patients with AIH who contracted COVID-19 were analysed. Seven patients who had previously undergone liver transplantation and three patients concomitantly diagnosed with AIH and COVID-19 were excluded (Figure 1). Our final study population included 254 AIH patients (79.5%, female) with a median age of 50 (range 17-85) years at the time of COVID-19. The general characteristics, clinical features and outcomes of the AIH patients with COVID-19 are presented in Table 1. The data of 110 patients have already been described in our previous study.[12]

At the last follow-up before contracting COVID-19, 199 (78.3%) patients had biochemical response to therapy while 55 (21.7%) were non-responders. Sixty-eight (26.8%) patients with AIH had features of cirrhosis. Co-morbid conditions were present in 107 (42.1%) of the patients.

The majority of patients (92.1%) were on immunosuppressive therapy at the time of COVID-19 diagnosis: 156 (61.4%) patients were on glucocorticoids alone or in combinations, 153 (60.2%) on thiopurines (azathioprine/6-mercaptopurine) alone or in combinations, 22 (8.7%) on MMF alone or in combinations and 16 (6.3%) on tacrolimus alone or in combinations. The median doses at the time of COVID-19 were: glucocorticoids (prednisolone equivalent) 5 mg/day (range 2.5-60); azathioprine 75 mg/day (range 25-200), MMF 1000 mg/day (range 500-2000) and tacrolimus 3 mg/day (range 2-7). Two patients received 50 mg/day of 6-mercaptopurin. Four patients were also receiving vedolizumab, infliximab and adalimumab. We excluded these patients from primary treatment analyses as these therapies were given for concomitant inflammatory disorders other than AIH.

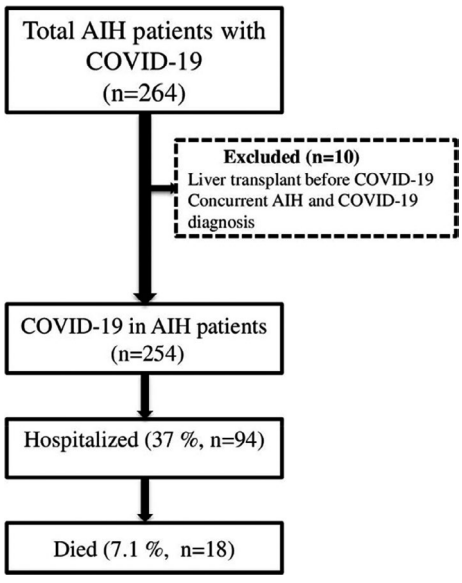

FIGURE 1 Study flow chart for patient inclusion

Most patients (n = 233, 91.7%) were symptomatic at the time of COVID-19 diagnosis; cough (n = 158, 62.2%) and fever (n = 150, 59.1%) were the most commonly reported symptoms. Gastrointestinal symptoms (abdominal pain, diarrhoea, nausea and vomiting) were noted in 59 (23.2%) patients.

3.2 | Management of patients with AIH during COVID-19

The doses of immunosuppressive therapy were modified (reduced or withdrawn) in 58 (22.8%) patients while therapy was maintained in 176 (69.3%) patients. A total of 118 (46.5%) patients received therapy for COVID-19. Antivirals (n = 58, 22.8%) and hydroxychloroquine (n = 39, 15.4%) were the most commonly prescribed therapies. High-dose steroid treatment was given to 35 (13.8%) patients and 86 (33.9%) patients received antibiotics. The details of COVID-19 therapies are presented in Table 1.

3.3 | Characteristics of AIH patients without immunosuppressive treatment

Twenty (7.9%) patients who were not taking any immunosuppressive drug at the onset of COVID-19 infection constituted the reference category for the primary analysis. Nine of these patients were in long-term remission and therapy was therefore discontinued by their physician, five patients had inactive cirrhosis, four patients had withdrawn therapy at their own discretion and two patients were non-responders to all previously administered therapies. All of these patients had at least an 8-week immunosuppression-free period prior to COVID-19 disease. The general characteristics of these 20 patients were similar to patients who were on immunosuppressive therapy during COVID-19 (Table S1).

3.4 | Outcomes of COVID-19 in patients with AIH

A total of 94 (37.0%) AIH patients were hospitalized during COVID-19. Among them, 76 (29.9%) patients required oxygen therapy via nasal cannula 47 (18.5%), non-invasive ventilation 18 (7.1%) or mechanical ventilation 11 (4.3%). Death was recorded in 18 (7.1%) patients. Detailed information regarding variables included in the full model analysis of COVID-19 severity is presented in Table S2. Crude, age-sex adjusted, and fully adjusted odds ratios with confidence intervals are presented in Table 2. These analyses indicate that patients on glucocorticoids (aOR 4.73, 95% CI 1.12-25.89) and patients receiving thiopurine treatment (aOR 4.78, 95% CI 1.33-23.50) were at an increased risk of worse COVID-19 severity compared to patients receiving no

TABLE 1 Demographics, clinical features and outcomes of study population (n = 254)

Median age, years (range)	50 (17-85)
Female, n (%)	202 (79.5)
Variant syndromes (PBC/PSC), n (%)	19 (7.5)/6(2.4)
AIH activity (remission), n (%)	199(78.3)
Presence of Cirrhosis, n (%)	68(26.8)
Smoking, n (%)	15(5.9)
Alcohol, n (%)	4(1.6)
Co-morbidity, (%)	107(42.1)
High blood pressure	62(24.4)
Diabetes mellitus	53(20.9)
Coronary artery disease	12(4.7)
Heart failure	4(1.6)
Respiratory disease	7(2.8)
Kidney insufficiency	8(3.1)
Active cancer	3(1.2)
AIH medications, n (%)	234(92.1)
AZA /6-MP alone	64(25.2)
AZA /6-MP +Glucocorticoids	85(33.5)
AZA /6-MP +Tacrolimus	1(0.4)
AZA /6-MP +Glucocorticoids + Tacrolimus	3(1.2)
Glucocorticoids alone	48(18.9)
Glucocorticoids +MMF	10(3.9)
Glucocorticoids +Tacrolimus	7(2.8)
Glucocorticoids +Methotrexate	1(0.4)
Glucocorticoids +MMF +Tacrolimus	2(0.8)
MMF alone	10(3.9)
Tacrolimus alone	3(1.2)
Symptoms at presentation, n (%)	233 (91.7)
Medical therapies used for COVID-19, n (%)	118 (46.5)
Antibiotics	86 (33.9)
Hydroxychloroquine	39 (15.4)
Antivirals	58(22.8)
Favipiravir	52(20.5)
Remdesivir	2 (0.8)
Lopinavir/Ritonavir	4 (1.6)
High-dose steroids	35 (13.8)
Anakinra	4 (1.2)
Tocilizumab	2 (0.8)
Intravenous immunoglobulin	2 (0.8)
Rituximab	1 (0.4)
Oseltamivir	1 (0.4)
Ivermectin	1 (0.4)
Oxygen therapy, n (%)	76 (29.9)
Nasal cannula	47 (18.5)
Non-invasive ventilation	18 (7.1)
Mechanical ventilation	11 (4.3)
Outcome of study population	
Hospitalized, n (%)	94(37.0)
Intensive care admission, n (%)	27(10.6)
Death, n (%)	18(7.1)

Abbreviations: AZA, azathioprine; MMF, mycophenolate mofetil; 6-MP, mercaptopurine; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

treatment both in unadjusted and adjusted models. Patients under both prednisolone-equivalent dose ≤5 mg/day (aOR 2.93, 95% CI 0.60-17.41) and >5 mg/day (aOR 8.30, 95% CI 1.72-50.22) were at increased risk of worse outcomes with a higher point estimate for high-dose corticosteroids. The odds ratio point estimates for MMF (aOR 3.56, 95% CI 0.76-20.56) and tacrolimus (aOR 4.09, 95% CI 0.69 to 27.00) were also similar to those of thiopurines and glucocorticoids but the confidence intervals could not reliably exclude a null effect. When we analysed the adjusted risk of COVID outcome related to AIH activity (remission vs. non-remission), the adjusted OR was 1.08 (95%CI 0.55-2.09) indicating that AIH disease activity was not associated with outcome.

4 | DISCUSSION

We investigated the impact of standard and non-standard immunosuppressive treatments on the clinical severity of COVID-19 in an international multi-centre dataset of 254 patients with AIH. Our study adds new information about the impact of baseline immunosuppressive medications on the risk of worse COVID-19 course in AIH patients. Patients who were on thiopurine and glucocorticoid therapy prior to the onset of COVID-19 had a higher risk of worse COVID-19 severity compared to patients with AIH who were not on immunosuppressive therapy. We also observed an association between MMF or tacrolimus use with worse COVID-19 course but wide confidence intervals in the analyses preclude reliable conclusions about these medications. The association between AIH medication and COVID-19 outcomes further supports the importance of preventive public health measures such as vaccination, social distancing and mask-wearing for patients with AIH during the COVID-19 pandemic.

A previous study on 58 immunosuppressive-treated AIH patients with COVID-19,[14] did not find an association between the use of immunosuppression and mortality. The limited number of patients in this study may have prevented powerful analyses. In our previous study on 110 AIH patients with COVID-19,[13] discontinuation or withdrawal of immunosuppression during COVID-19 was not associated with a reduced risk of severe COVID-19 outcome. This observation should perhaps not be surprising considering that the immunosuppressive effect of AIH medications persists several weeks after their discontinuation. Similar to previous analyses of AIH-COVID-19 data,[13,14] the presence of cirrhosis and other comorbidities were associated with worse COVID-19 outcomes in the current study. The odds ratios for cirrhosis and comorbidities should however be interpreted with caution, since

TABLE 2 Crude and adjusted OR for worse COVID-19 severity according to AIH medications

	OR Crude (95% CI)	OR Age-sex adjusted (95% CI)	OR fully adjusted (95% CI)
Glucocorticoids	4.49 (1.31-20.89)	3.92 (1.13-18.40)	4.73 (1.12-25.89)
Thiopurines	3.27 (1.04-14.45)	3.22 (1.02-14.28)	4.78 (1.33-23.50)
MMF	3.06 (0.74-15.88)	3.58 (0.85-18.78)	3.56 (0.76-20.56)
Tacrolimus	1.72 (0.32-10.05)	2.30 (0.42-13.75)	4.09 (0.69-27.00)

Note: Odds ratios are from an ordinal logistic regression model and indicate the relative risk of being in a worse outcome category compared to no treatment. In the fully adjusted model, additional adjustments were made for the number of comorbidities (Table 1), presence of cirrhosis and combinations of treatment.

these variables were used for adjustments in the primary analysis and carry a risk of bias when interpreted on their own.[16]

Thiopurines are also commonly used in the treatment of IBD. A recent analysis of the large SECURE-IBD data showed that thiopurine therapy was significantly associated with severe COVID-19.[9] The median dose of thiopurine therapy in our patients was 75 mg/day which is lower than what is often used for IBD. Despite the lower dose, we found that thiopurine was associated with an increased risk of worse COVID-19 course also in AIH patients.

Systemic glucocorticoids were associated with higher odds of worse COVID-19 severity in patients with AIH. A recent large cohort study of 6077 patients with immune-mediated inflammatory diseases showed that baseline glucocorticoid use was significantly associated with adverse COVID-19 outcomes (OR per 1 mg increase in prednisone-equivalent glucocorticoid dose was 1.07; 95% CI, 1.05-1.08).[17] We also observed a similar trend indicating a lower point estimate for low dose glucocorticoids (prednisolone-equivalent ≤5 mg/day) compared to that of higher dose (>5 mg/day) glucocorticoid use, albeit with far more uncertainty. These results also support the notion of aiming for maintenance of remission with the lowest effective glucocorticoid dose in AIH patients during the COVID-19 pandemic.

The relationship between MMF or tacrolimus use and COVID-19 outcomes has mainly been studied in liver transplant recipients. The overall effect of these immunosuppressive agents on the COVID-19 outcomes remains inconclusive. Two studies showed that both MMF and tacrolimus have no impact on COVID-19 outcomes.[18,19] In contrast, one study reported that MMF use was an independent predictor of severe COVID-19,[10] while another study reported that tacrolimus use was associated with better survival in liver transplant receipts with COVID-19.[11] A recent large Danish cohort study showed that cyclosporine/tacrolimus treated patients (for any reason) had a significantly higher risk of hospitalization for COVID-19 when compared to the general population.[20] Our results do not exclude the possibility of an association between baseline use of MMF or tacrolimus and a worse COVID-19 course in patients with AIH.

The COVID-19 related mortality rate was 7.1% in our cohort of patients with AIH. In two previous AIH-COVID-19 studies,[13,14] mortality rates were 10% and 23%. The frequency of cirrhosis (26%) in this study population was lower than reported in two previous studies (29%-54%). The rates of age >65 years, co-morbidity and cirrhosis were higher in our smaller previous study[13] and more patients in the present larger study received therapy for COVID-19 (Table S3). These factors may explain the lower mortality rate in the current study. We did not find association between AIH activity and COVID-19 severity. Two previous studies found similar mortality rates among AIH patients and those with other causes of chronic liver diseases.[13,14] Our study aim was to evaluate any associations between AIH medications and clinical courses of COVID-19. We therefore did not include a control group of patients with other causes of chronic liver diseases. Instead, we used AIH patients who were not on immunosuppressive treatment during COVID-19 as the reference category of the treatment spectrum. This analysis allowed examining the impact of AIH medications itself on the severity of COVID-19.

We here report the largest cohort to date of patients with AIH affected by COVID-19. The study was performed through an international multi-centre effort and collected data from geographically diverse areas in Europe and both Americas. We used a graded severity scale to estimate the association of immunosuppressive drugs and COVID-19 severity.[15] This clinical progression scale of COVID-19 that we used was proposed by the WHO and is commonly used in clinical trials evaluating COVID-19 therapeutics. Further, reporting directly by hepatologists following the patients strengthens the validity of our data.

The retrospective nature of our study is the main limitation. Potential confounders may therefore affect our results. We acknowledge that management and therapeutic strategies for COVID-19 vary between centres and countries. Patients with mild COVID-19 disease were possibly less likely to be included in our study as those with severe COVID-19 are more likely to come to the attention of their hepatologists. Also, COVID-19 testing is more likely directed towards severely symptomatic cases. These factors may have led to a study sample of more severe COVID-19 cases. The AIH cohort is however representative of that of AIH-specific registries, with 80% female patients, 92% on immunosuppressive therapy and 27% having cirrhosis.

In conclusion, baseline use of thiopurines (azathioprine or 6-mercaptopurine) and glucocorticoids were associated with a higher risk of worse COVID-19 severity compared to no treatment for AIH. Our data also suggest that MMF and tacrolimus therapy may be associated with worse COVID-19 course, but this association requires validation in larger AIH cohorts.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

AUTHOR CONTRIBUTIONS

CE, SW, TDS, RD and ER conceptualized the study. CE, RD, BE, KT, SW and ER collected and analysed data. CE, RD, CL, BE, FHT, CA, ARÇ, MP, LC, HM, MAC, TP, CR, AJGA, NK, HK, LN, SF, KI, ZME, MMA, MA, YB, KA, AG, EB, FE, AU, BM, NE, ND, RS, RMC, MH, IH, MK, MM, MS, MRAS, TE, BM, SB, EL, GMZ, ADB, MA, AHB, EDM, SY, AY, MB, GCN, EKA, MV, FG, ECR, NKG, YÜ, JB, NCEV, FGU, SRG, JA, MA, NR, AF, SF, SKS, GND, EMY, RI, MS, JPHD, DA, EB, JLB, PI, CL, ER and SW contributed data. CE, RD, TDS, KT, ER, and SW interpreted data and prepared manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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