



Review Article

Special Considerations in the Management of Autoimmune Hepatitis in COVID-19 Hotspots: A Review

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Abstract

The ongoing coronavirus disease-2019 (COVID-19) pandemic has necessitated special considerations in the management of diseases. The way presence of pre-existing diseases or treatment for it predisposes to, alters course of, and changes the management of COVID-19, is of relevance and is being extensively studied. Autoimmune hepatitis (AIH) is unique in that it is an autoimmune disease mandating treatment with immunosuppressive drugs, as well as a liver disease with potential for varying degrees of underlying fibrosis. The use of immunosuppressive drugs could alter the risk of acquiring COVID-19, the clinical course and severity of COVID-19 and the degree of underlying liver fibrosis could alter the clinical outcomes of patients with COVID-19. In this review, we try to summarize key areas relevant in understanding and improving the clinical care of patients with AIH in the current pandemic. Special considerations required in the management of patients with AIH in COVID-19 hotspots have been outlined based on the current evidence.

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Introduction

First noticed as a cluster of viral pneumonia among people known to have visited a market in the Wuhan City of Hubei

Keywords: Hepatitis; Autoimmune; Liver cirrhosis; COVID-19; SARS-CoV-2 infection; Immunosuppressive agents.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACLF, acute on chronic liver failure; AD, acute decompensation; AIH, autoimmune hepatitis; ALF, acute liver failure; APASL, Asia Pacific Association for Study of Liver; CNIs, calcineurin inhibitors; COVID-19, coronavirus disease-2019; DILI, drug-induced liver injury; EASL, European Association for Study of Liver; IBD, inflammatory bowel diseases; MMF, mycophenolate mofetil; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; WHO, World Health Organization.

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province in China,¹ and later on investigated by the China Center for Disease Control and Prevention and found to be due to infection with a new beta coronavirus,² the disease was later named Coronavirus disease-2019 (COVID-19),³ and the virus causing it was christened severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).⁴ The disease spread throughout the world over a period of a few months, to be declared as a pandemic by the World Health Organization (WHO) on the 11th of March 2020.⁵ By the 30th of December 2020, it had infected over 80 million people and resulted in the death of over 1.7 million people.⁶ While predominantly a respiratory pathogen, SARS-CoV-2 has also been shown to cause significant neurologic, cardiac, gastrointestinal, hepatic, renal, hematologic, obstetric, gynecologic, and rheumatologic abnormalities as well.⁷

The focus of this review is on special considerations for the management of autoimmune hepatitis (AIH) in areas with widespread community transmission of COVID-19. Factors that need to be considered include the risk of acquiring COVID-19 and the risk of poor outcomes with COVID-19. Outcomes in patients with COVID-19 could be altered due to AIH itself, because of the immunosuppressive medicines used to treat AIH, or by virtue of liver impairment that AIH has caused. We will be discussing aspects that are of specific relevance to a practitioner caring for AIH in COVID-19 hotspots. Relevant aspects of COVID-19-induced liver injury, aspects of COVID-19 prevention (including vaccination), and special considerations required in the management of AIH have been discussed herein. We have also discussed possible approaches that a clinician can adopt in various case-scenarios that may be encountered.

Liver injury in COVID-19

Liver abnormalities noted to be present in patients having COVID-19 include transaminitis, hyperbilirubinemia and hypoalbuminemia.^{8–11} These abnormalities are thought to occur by one or more of the following several mechanisms (Fig. 1): direct cytopathy;¹² immune-mediated;¹³ 3. hypoxia-related;¹⁴ drug-induced;¹⁴ and, microvascular thrombosis.^{15,16} Patients with COVID-19 and liver injury,¹⁷ as well as those with prior hepatic comorbidities, have been shown to have poor outcomes with COVID-19.¹⁸ Patients with cirrhosis are thought to be at moderate risk, whereas patients with decompensated cirrhosis are at high risk of poor outcomes with COVID-19.

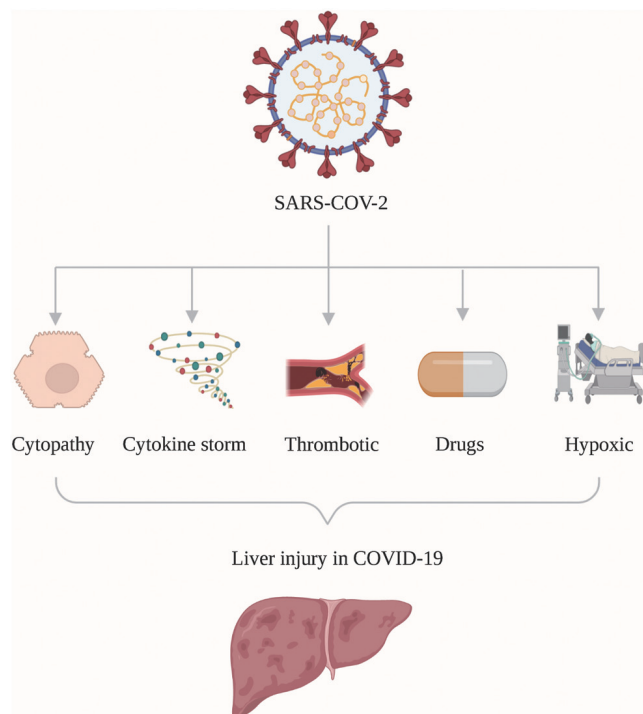


Fig. 1. Pathogenesis of liver injury in COVID-19.

Direct cytopathy

ACE2 receptors, which the SARS-CoV-2 virus utilizes for entering cells have been shown to be expressed in cholangiocytes¹⁹ and probably hepatocytes²⁰ as well. It has also been shown that SARS-CoV-2 invades liver cells and causes cytopathy.¹² This may, at least partially, be responsible for the hepatic dysfunction seen in COVID-19 patients.¹²

Immune-mediated

SARS-CoV-2 infection results in a disordered inflammatory response, i.e. the cytokine storm,²¹ with increase in pro-inflammatory cytokines. This has been shown to be responsible for severe pulmonary and extrapulmonary dysfunction, including liver injury. Liver dysfunction has been shown to be particularly more in patients with increased levels of inflammatory markers, such as CRP, TNF and IL-6.¹³

Hypoxic/ischemic

In severe COVID-19, multiorgan dysfunction can lead to hypoxia-related to acute-respiratory distress syndrome,²² hypotension,²³ or congestive cardiac failure. All of these can result in liver dysfunction.²⁴

Drug-induced liver injury (DILI)

In addition to supportive therapy, antivirals, immunomodulators and antithrombotic drugs are used in the management of COVID-19. Several of these drugs, including antivirals such as lopinavir-ritonavir, remdesivir, favipiravir etc., and immunomodulators such as tocilizumab, baricitinib, etc.

may cause liver dysfunction.^{25,26}

Microvascular thrombosis

Endothelial dysfunction along with inflammation in patients with COVID-19 produces vascular thrombosis in multiple organs.²⁷ Elevated D-dimer levels were found to be independently associated with liver dysfunction in one study,¹⁵ which could point to an association of thrombosis with liver dysfunction. Studies of liver biopsies from patients with COVID-19 and liver dysfunction have shown significant microvascular thrombosis which could lead to liver dysfunction.¹⁶ This could point to a contribution by microvascular thrombosis to the liver dysfunction seen in patients with COVID-19.

Pre-existing liver diseases and COVID-19

Patients with AIH have varying degrees of underlying fibrosis and as much as 40% of these patients develop cirrhosis.²⁸ The degree of underlying fibrosis in patients with AIH has the potential to have an effect on the risk of acquiring COVID-19, as well as on clinical outcomes in patients with COVID-19.

It can be assumed that, despite a reduction in the immunity of patients with cirrhosis, the risk of acquiring COVID-19 does not seem to be higher in patients with cirrhosis, as evidenced by the results of a meta-analysis which demonstrated that the prevalence of cirrhosis in patients with COVID-19 is similar to that in the COVID-19-negative population.¹⁸

There seems to be an upregulation of ACE2 receptors in the liver, which probably makes patients with cirrhosis more vulnerable to COVID-19-related liver injury.²⁹ Patients with pre-existing liver disease have been shown to have increased mortality and morbidity, with COVID-19.¹⁸ Multiple studies have found deterioration of liver functions and decompensation in cirrhotic patients with COVID-19.³⁰⁻³² Patients were found to have significantly higher risk of mortality with worsening Child-Pugh status.^{31,32} Cirrhosis was also found to be an independent predictor of severe COVID-19, in patients with AIH in recent multicenter studies.^{33,34} With such poor outcomes, it becomes pertinent that patients with cirrhosis be considered high risk.

Immunosuppressants and COVID-19

Patients on immunosuppressants have a complex interplay of factors in favor of and against SARS-CoV-2. On one hand, immunomodulators such as mycophenolate mofetil (MMF)^{35,36} and calcineurin inhibitors (CNIs) like tacrolimus³⁷ and cyclosporine^{38,39} have been demonstrated to have antiviral activity against coronaviruses, and glucocorticoids administered for COVID-19 have been shown to prevent the disordered immune response that is responsible for poor outcomes in COVID-19.⁴⁰ On the other hand, the immunosuppression attributable to these drugs may cause increased susceptibility to SARS-CoV-2 infection,⁴¹ secondary bacterial or fungal infections, and prolongation of viral clearance.⁴² There have been studies that demonstrated increased risk⁴¹ as well as others that demonstrated average risk⁴³ of acquiring SARS-CoV-2 infection for patients on immunosuppressants, and the question largely remains unresolved to date. Retrospective studies have demonstrated a risk of bacterial superinfection⁴⁴ or increased use of antibiotics⁴⁵ in patients managed with steroids for COVID-19, whereas randomized controlled trials have negated this⁴⁶⁻⁴⁸ as an adverse event

Table 1. Published data of AIH patients with COVID

Study	Region	Number of COVID-19-positive AIH	COVID-19 requiring hospitalization	Survived
Verhelst 2021 ⁵⁰	Flanders, Belgium	1	100% (1/1)	100% (1/1)
Rigamonti 2020 ⁵¹	Northern Italy	4	50% (2/4)	100% (4/4)
Di Giorgio 2020 ⁵²	Northern Italy	4	50% (2/4)	75% (3/4)
Gerussi 2020 ⁵³	Italy	10	60% (6/10)	90% (9/10)
Marjot 2021 ³⁴	Multinational	70	76% (53/70)	77% (54/70)
Efe 2021 ³³	Multinational	110	46% (51/110)	90% (99/110)

of steroids. The data on the effect of steroids on viral shedding is mixed; although, the wealth of evidence suggests that low-dose steroids are not associated with any increase in viral shedding.⁴² Studies have also been performed to assess how these seemingly opposing actions translate to clinical outcomes in COVID-19. The risk of acquiring SARS-CoV-2 infection seems to be higher in patients with autoimmune diseases on steroids⁴⁹ and clinical outcomes seem to be worse in patients on steroids as well as in patients on immunomodulators, in patients with autoimmune diseases.⁴⁹ Early data available specifically in the context of AIH seem to show that continued immunosuppression does not lead to poor outcomes with COVID-19.^{33,34}

AIH and COVID-19

Two large multicenter studies have addressed the impact of COVID-19 in patients with AIH.^{33,34} In both the studies, the outcomes of patients with AIH were compared with a cohort of non-AIH patients with chronic liver disease. The consistent findings across both the studies was that there is no increase in severity of COVID-19 infection across patients with AIH compared to other etiologies of chronic liver disease.^{33,34} Presence of cirrhosis, particularly Child-C disease, was the most significant factor of poor outcomes in these patients.³⁴ New-onset liver injury was seen in one-third of the patients with AIH after COVID-19 in one study.³³ However, the use of immunosuppressants was not associated with poor outcomes in patients with AIH and COVID-19.³³ In fact, one study showed that continuation of immunosuppression was associated with lower risk of new-onset liver injury.³³ This suggests that immunosuppression needs to be continued in patients with AIH and COVID-19. Apart from these two studies, however, data on AIH and COVID-19 are limited to a few small case series (Table 1).⁵⁰⁻⁵³

Diagnostic approach

The diagnostic approach for AIH in COVID-19 hotspots can be the same as elsewhere, broadly speaking. Selected patients who are asymptomatic and being evaluated for abnormal transaminases or only mildly symptomatic for AIH can be, in the initial part of the diagnostic workup, evaluated by a telemedicine-based approach. Liver biopsy is necessary for a diagnosis of AIH to be made, as per American Association for the Study of Liver Diseases (AASLD) guidelines⁵⁴ and can be performed in a COVID-minimal pathway, safely, for COVID-19-negative patients. Liver biopsy in COVID-19-positive patients need to be decided on a case-by-case basis, depending on the urgency to treat AIH, the severity of COVID-19, and other factors like the presence of coagulopathy, sepsis, logistics, chance of cross-infection, etc. The Asia Pacific Association for Study of Liver (APASL)

recommends liver biopsy in COVID-19-negative patients when autoimmune flare is suspected and advises against liver biopsy in COVID-19-positive patients.⁵⁵

Prevention of COVID-19

General measures

Owing to the high risk of poor outcomes that can be expected with the degree of pre-existing liver dysfunction and immunosuppression, prevention of SARS-CoV-2 infection is extremely important in patients with AIH. The preventive strategy against COVID-19 should comprise general measures as well as vaccination. General measures should involve measures to be adopted by the patient,⁵⁶ hospital-designed infrastructure measures,⁵⁷ and hospital operational measures,⁵⁷ which include a COVID-minimal pathway,⁵⁸ as well as measures to be adopted by health-care personnel.⁵⁹ Telemedicine becomes particularly relevant during the current COVID-19 epidemic as it has the potential to reduce the need for hospital visits, which in turn reduces the chance of crowding in hospital outpatient clinics, thereby reducing the risk of spreading SARS-CoV-2.⁶⁰ Telemedicine has been evaluated specifically in the context of management of AIH during the COVID-19 pandemic and has been shown to improve patient adherence to therapy thereby minimizing the chances of relapse, as compared to the standard care group.⁶⁰

Vaccination

As on December 23rd, 2020, there have been at least seven COVID-19 vaccines⁶¹ licensed in different parts of the world and over 200 vaccines in different stages of development.⁶² In the context of patients with AIH, four specific aspects need to be addressed; these include: 1) safety of the vaccine in patients on immunosuppressants; 2) safety of the vaccine in patients with liver diseases; 3) efficacy of the vaccine in patients on immunosuppressants; and, 4) efficacy of the vaccine in patients with liver diseases.

As far as the licensed vaccines are concerned, patients on immunosuppression were excluded from vaccine licensing trials. While some trials included a small number of patients with pre-existing liver diseases, patients with advanced liver diseases were still excluded and no subgroup analysis was performed to assess outcomes or adverse events specifically in patients with liver diseases.⁶³ Thus, it is not clear at this moment how safe and effective these vaccines would be, in standard doses, for patients with AIH, especially while on immunosuppressive medications. Extrapolating from the experience with vaccination for other diseases in patients with liver diseases,⁶⁴⁻⁶⁶ in patients on immunosuppression,⁶⁷ and specifically in AIH,⁶⁸ the likely efficacy of the

Table 2. Special considerations in the management of AIH in COVID-19 hotspots: A suggested approach

COVID-19 status	AIH status	Special considerations
COVID-19-negative	Diagnosis of AIH	Diagnostic algorithm same as otherwise. Liver biopsy to be planned in COVID-minimal pathway
	Newly diagnosed patients with activity	Steroids and azathioprine can be given as indicated otherwise. Budesonide to be preferred over prednisolone in appropriate situations, in noncirrhotic patients, and in patients without acute severe AIH
	Patients in remission	Continue immunosuppressant at lowest recommended dose required to maintain remission. Decision to stop immunosuppression to be made in patients who have had long-term remission, as per latest guidelines for AIH. Telemedicine-based follow-up in appropriate cases
	Patients who require start of second-line agent	CNIs (tacrolimus) may be preferred over mycophenolate in patients with no other contraindications ^a
	Patients who require start of third-line agent	Infliximab may be preferred over rituximab in patients with no other contraindications ^a
	Decompensated cirrhosis	Treatment algorithm same as otherwise. Living donor liver transplant to be considered for urgent/emergency indications only
	Acute severe AIH ALF due to AIH	Diagnostic and treatment algorithm same as otherwise Diagnostic and treatment algorithm same as otherwise. May require urgent liver transplantation
COVID-19-positive	Diagnosis of AIH	Evaluation by serology, imaging same as otherwise. Decisions regarding liver biopsy to be taken on case-by-case basis
	Newly diagnosed patients with activity/patients in remission/patients who require start of second-line agents/patients who require start of third-line agents/patients with decompensated cirrhosis	Decisions regarding management to be taken on an individualized, case-by-case basis. Patients with AIH in remission may continue immunosuppressants as before, unless other contraindications or considerations are present. Treatment decisions in patients requiring induction or escalation of therapy for AIH needs to be taken on a multidisciplinary, case-by-case basis
	Acute severe AIH	Need for aggressive immunosuppression likely to override all other considerations, final decision to be taken on a multidisciplinary, case-by-case basis
	ALF due to AIH	Decision to be taken on a multidisciplinary, case-by-case basis

^aWeak suggestion, based on data extrapolated from other conditions.

COVID-19 vaccine in this subgroup of patients is likely to be lower compared to the normal healthy adult.

Considering the high risk of poor outcomes due to COVID-19 infection in patients with liver diseases¹⁸ and patients with immunosuppression,⁶⁹ the benefits of vaccination may outweigh the risks. COVID-19 vaccination is being suggested in patients with chronic liver disease and solid organ transplant recipients on immunosuppression by various international societies, including AASLD⁶³ and European Association for Study of Liver (EASL).⁷⁰ Till further data on safety and efficacy are available, COVID-19 vaccines need to be administered at standard doses, unless other contraindications are present. Due to the high risk of adverse events, live vaccines⁷¹ and replicating viral vector vaccines⁷² are best avoided in patients on immunosuppressive medications. Further, household members and care providers of these patients should also receive vaccination while continuing appropriate use of masks, sanitizers and social distancing — the keystone of protection against COVID-19. EASL and APASL recommend patients with AIH to be also vaccinated against influenza and *Streptococcus pneumoniae*.^{55,73} The formation of neutralizing antibodies in liver transplant recipients (especially those receiving immunosuppressants) have been suboptimal, as shown by a recent study.⁷⁴ The clinical impact of this suboptimal response remains to be

seen. However, this should not deter any clinician from prescribing the vaccine in these patients.

Treatment in COVID-19 negative patients

Principles of treatment

It is clear that the presence of pre-existing liver disease has a significant bearing on the outcomes of patients with COVID-19,¹⁸ and given the fact that the present pandemic has been ongoing for the past several months and will continue to do so for some time, it seems prudent that the patients not having active COVID-19 but requiring induction or maintenance therapy for AIH be given immunosuppression as required because withdrawing, delaying or denying it may result in worsening fibrosis or cirrhosis.⁷⁵⁻⁷⁷ Recommendations by APASL⁵⁵ and the EASL⁷³ seem to support the view that immunosuppression needs to be continued. Strategies for treatment and follow-up should incorporate aspects of prevention as elaborated, including general measures and vaccination. We have discussed special considerations required in the treatment of COVID-19-negative patients with AIH below, and summarized them in Table 2.

Decisions for patients with active COVID-19 requiring immunosuppression for AIH induction or maintenance need to be considered on an individualized, case-by-case basis after assessing risks and benefits.

First-line agents

Patients on systemic steroids have been found to have poor COVID-19-related outcomes.⁴⁹ Prednisolone/prednisone or budesonide in combination with azathioprine is used for first-line management of AIH.⁵⁴ Owing to high first pass metabolism of budesonide, it is known to have less systemic toxicity and less chance of infections.⁷⁸ It seems reasonable that patients with new diagnosis of AIH, no cirrhosis and no acute severe AIH be considered for budesonide over prednisolone especially, as it has been proven to have a higher efficacy,⁷⁸ and it is biologically plausible that patients on budesonide may fare better than patients on prednisolone, if infected with SARS-CoV-2.

Data from inflammatory bowel diseases (IBD)⁷⁹ show that thiopurine monotherapy is associated with poor COVID-19 outcomes. Data regarding the safety of azathioprine specifically in AIH in the context of COVID-19, however, is not available, even though two studies had shown that continuation of immunosuppressive medicines in AIH is not associated with poor outcomes with COVID-19.^{33,34} Azathioprine still remains the first-line agent of choice as an immunomodulator, till conclusive evidence regarding an alternate first-line agent with better overall outcomes is available.

Second-line agents

Second-line agents for the management of AIH include MMF as well as CNIs, such as tacrolimus and cyclosporine.⁵⁴ As far as AIH-related outcomes are concerned, MMF and tacrolimus are equivalent.⁵⁴ Although specific data on AIH patients treated with these medicines and COVID-19-related outcomes are not available, data of safety of these same drugs used in other diseases, in terms of COVID-19-related outcomes, may be cautiously extrapolated to AIH, till specific data are available. In solid organ transplant patients, treatment with mycophenolate has been shown to be risky in a dose-dependent manner,⁸⁰ but that with CNIs appears to not be.^{80,81} It would therefore seem appropriate that tacrolimus should be preferred over MMF when no other contraindications are present.

Third-line/salvage agents

Salvage options or third-line agents described by the AASLD guideline for AIH include infliximab and rituximab.⁵⁴ Being an anti-TNF agent, infliximab has a potential to mitigate the cytokine storm, which is a crucial part of the pathogenesis of COVID-19.⁸² Studies in IBD⁸³ and in rheumatology⁸⁴ have shown that anti-TNF drugs are not associated with worse outcomes in COVID-19. Concerns have been expressed regarding risk of poor outcomes for patients on rituximab,⁸⁵ and early evidence suggests this as well.⁸⁶ Till conclusive evidence that supports safety in this regard is available, it is better to consider other third-line/salvage agents, such as infliximab, over rituximab, whenever possible.

Overlap syndromes

In addition to the immunosuppressants described above,

patients with overlap syndromes may also require ursodeoxycholic acid.⁵⁴ There is no reason to have concerns regarding the use of this agent in the context of the current COVID-19 pandemic. In fact, ursodeoxycholic acid is an agent with potential to have benefits in the treatment of COVID-19 as well.⁸⁷ Till evidence to the contrary is available, treatment with this agent can be initiated or continued as indicated.

Liver transplant

Liver transplant is indicated in patients with AIH who present with acute liver failure (commonly referred to as ALF) or as salvage in acute severe AIH or in cirrhosis with decompensation.⁵⁴ In the presence of widespread community transmission of COVID-19, considerations for liver transplant should consider appropriate local guidelines which specifically discuss this aspect. In view of the risk to donors, living donor liver transplantation is best restricted to urgent indications.⁸⁸

Management of AIH in COVID-19 patients

The management of AIH in COVID-19-positive patients would require decisions to be taken on a multidisciplinary, case-by-case basis. Decisions should be based on a multitude of factors, such as urgency to treat AIH, severity of COVID-19, presence of co-existing sepsis, requirement of drugs for COVID-19 that may have interactions with drugs given for AIH, etc. APASL recommends continuing immunosuppression in patients with mild COVID-19.⁵⁵ Data from two multinational studies are available which show no benefit of withdrawing immunosuppression in patients with AIH and active COVID-19.^{33,34} One study even showed that continuation of immunosuppression lowered the risk of new-onset liver injury.³³ The exact reasons for stopping immunosuppression in these studies are not known. The numbers of patients on high-dose steroids and MMF were low in these studies, for meaningful conclusions to be made. However, these studies do support the continuation of immunosuppression in patients with AIH and COVID-19. Some special considerations required while managing patients with AIH who also have COVID-19 are summarized in Table 2.

Drug interactions are particularly important while managing patients with COVID-19 and AIH. Management of COVID-19 is constantly being revised with a variety of drugs being tried for its treatment, with varying efficacy. New data are emerging every day and with the introduction of new drugs, one needs to be aware of the side effect profile of the drugs being used and their potential interaction with the concomitant medications being used for the management of comorbid conditions. Interactions between drugs used for immunosuppression, such as CNIs, may have significant drug interactions, which, if not paid attention to, can be deleterious.⁸⁹ We have listed the interactions between the drugs used for the management of COVID-19 and the drugs used in AIH in the table below (Table 3). As to the optimal treatment and drugs for COVID-19, the data are still evolving; however, it is suggested to check the side effect profile and drug interactions of the drug being used. One such useful updated resource to check for drug interactions is <https://www.covid19-druginteractions.org/checker>.

Conclusions

Management of auto-immune hepatitis in areas with wide-

Table 3. Drug interactions between immunosuppressants used for management of AIH and drugs used for management of COVID-19

Drug type	Azathioprine	MMF	Tacrolimus	Cyclosporine
Interferons				
Interferon-alpha	Potential additive hematological toxicity	No interaction	No interaction	No interaction
Interferon0beta	Potential additive hematological toxicity	No interaction	No interaction	No interaction
Antivirals				
Favipiravir	No interaction	No interaction	No interaction	No interaction
Lopinavir-ritonavir	No interaction	Potential altered drug levels of mycophenolate; Drug level monitoring recommended	Increased levels of tacrolimus; Risk of QT prolongation	Increased plasma levels of cyclosporine; Drug monitoring recommended
Remdesivir	No interaction	No interaction	No interaction	No interaction
Ribavirin	Potential additive hematological toxicity	No interaction	No interaction	No interaction
Nitazoxanide	No interaction	No interaction	No interaction	No interaction
Antimalarials				
Chloroquine	Potential additive hematological toxicity	No interaction	Increased levels of tacrolimus; Risk of QT prolongation	Increased plasma levels of cyclosporine; Drug monitoring recommended
Hydroxychloroquine	Potential additive hematological toxicity	No interaction	Increased levels of tacrolimus; Risk of QT prolongation	Increased plasma levels of cyclosporine; Drug monitoring recommended
Monoclonal antibody				
Tocilizumab	Potential additive hematological toxicity	No interaction	Monitoring of tacrolimus drug levels recommended	Monitoring of cyclosporine drug levels recommended
Bamlanivimab	No interaction	No interaction	No interaction	No interaction
Canakinumab	Potential additive hematological toxicity	No interaction	Monitoring of tacrolimus drug levels recommended	Monitoring of cyclosporine drug levels recommended
Sarilumab	Potential additive hematological toxicity	No interaction	Monitoring of tacrolimus drug levels recommended	Monitoring of cyclosporine drug levels recommended

spread community transmission of COVID-19 needs special considerations in the diagnostic approach, preventive aspects and treatment. The management of immunosuppression is particularly complex in this set of patients and specific data in the context of AIH in COVID-19 are lacking. Management of immunosuppression in patients with AIH in COVID-19 hotspots requires a tailored approach based on data from relatively small observational studies and from data extrapolated from other auto-immune diseases till better evidence is available. The management of AIH in patients diagnosed with COVID-19 requires a multidisciplinary approach with decisions considered on a case-by-case basis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (DM, SS, AS), acquisition of data (DM, AA, SS), drafting of the manuscript (DM, SS, AA), critical revision of the manuscript for important intellectual content (DM, AA, SS, AS), administrative support, study

supervision (AS).

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