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CASE REPORT | LIVER

Role of Sirolimus and Rituximab in the Treatment of Autoimmune Hepatitis

Spyridon Zouridis, MD[1], Ye H. Oo, MBBS, PhD[2], and Wing-Kin Syn, MD, PhD[1,3]

[1]*Division of Gastroenterology and Hepatology, Department of Medicine, Saint Louis University Hospital, St Louis, MO*
[2]*Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK*
[3]*Department of Physiology, Faculty of Medicine and Nursing, University of Basque Country UPV/EHU, Vizcaya, Spain*

ABSTRACT

Autoimmune hepatitis (AIH) is a rare chronic liver disease affecting annually 100,000-200,000 individuals in the United States. The first-line therapy in AIH is azathioprine and corticosteroids. However, adverse events may occur, which can preclude disease remission. In these cases, mycophenolate, mercaptopurine, and tacrolimus can be used. Rituximab is offered in difficult to treat cases. Sirolimus is an alternative regimen. However, little is known about its use in AIH. This is a challenging case of "difficult to treat" AIH managed with sirolimus and rituximab, after multiple unsuccessful trials with other medications.

KEYWORDS: autoimmune hepatitis; sirolimus; liver; rituximab; autoimmune liver disease

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare liver disease of unknown etiology. It is characterized by chronic, progressive immune-mediated liver inflammation affecting 100,000-200,000 individuals yearly in the United States.[1] The clinical presentation widely varies from fulminant hepatitis to one-fourth of AIH patients being asymptomatic.[1] For its diagnosis, a thorough strategy is followed, including exclusion of other chronic liver diseases, evaluation of liver biochemistry, and autoimmune serologic markers. Liver biopsy findings include interface hepatitis, rosettes, and plasma cells.[1] Therapy is offered in all patients with significantly abnormal liver biochemistry, presence of necroinflammation, and/or fibrosis on biopsy.[1] The standard treatment includes azathioprine (AZA) and corticosteroids to achieve complete biochemical remission within 6 months.[1] For patients not tolerating AZA, mercaptopurine and mycophenolate mofetil (MMF) are options. Tacrolimus is third-line treatment. However, MMF is not suitable for young patients with family plans, and tacrolimus is limited to patients with normal renal function. Up to 10%–20% have inadequate response on second- and third-line treatment, and 5%–10% report side effects with these medications.[2] Sirolimus is an alternative option in difficult to treat AIH patients; however, the experience with this is very limited.[3] This is a case of difficult to control AIH under sirolimus and rituximab treatment.

CASE REPORT

A 23-year-old woman with AIH presented to our institution for transition of care. The patient had been diagnosed with AIH during childhood. Diagnosis was established at that time by liver biopsy and biochemical markers providing an overall International AIH Group score of 20. Broad workup excluded other causes of liver injury, including viral hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, Wilson disease, hemochromatosis, celiac disease, and a-1 antitrypsin deficiency. Of note that markers such as soluble liver antigen antibodies, liver kidney microsomal (LKM)/antimitochondrial antibodies, immunoglobulin M, A-1 antityrpsin, and ceruloplasmin were found negative at diagnosis and later on re-evaluation. At the time of initial diagnosis, the liver biopsy revealed severe chronic inflammation expanding the portal tracts, pericellular collagen, and bridging. Despite an elevation in alkaline phosphatase, patient did not meet Paris criteria for overlap syndrome, given the lack of evidence of primary biliary cholangitis in the biopsy and negative antimitochondrial antibodies. At the time of initial diagnosis, magnetic resonance cholangiopancreatography showed evidence of moderate/severe hepatic fibrosis but no

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Correspondence: Spyridon Zouridis, MD (spzourds@gmail.com).

Table 1. Liver biochemistry, IgG, and sirolimus treatment

Date	October 2018	October 2019	February 2020	May 2020	March 2021	February 2022	May 2023
ALT (IU/L)	949	161	83	104	38	68	35
AST (IU/L)	741	221	83	97	41	74	38
T Bili/D Bili (mg/dL)	0.6/–	0.4/–	0.4/0.2	0.5/0.2	0.5/0.1	0.3/0.2	0.4/–
ALP (IU/L)	178	216	194	201	122	203	114
IgG (mg/dL)	—	—	1,860	—	1,730	1,640	1,416

Date	October 2018	September 2019	February 2020	May 2020	May 2021	February 2022	May 2023
Sirolimus daily dose (mg)	4	3	3	4	4	4	4
Sirolimus level (ng/mL)	—	—	19.4 (not trough/random)	14.3 (unknown if trough)	2 (trough)	3.3 (trough)	<1 (trough)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; D Bili, direct bilirubin; IgG, Immunoglobulin G; T Bili, total bilirubin.

intrabiliary or extrabiliary tree abnormalities. When the patient was evaluated in the clinic, years after diagnosis was also under treatment with hydroxychloroquine and meloxicam for arthritis.

The patient was placed on AZA and high-dose corticosteroid therapy on diagnosis. However, liver biochemistry never normalized, and MMF was added 1 year later. The patient stayed on this combination for almost 2 years, while she suffered multiple AIH exacerbations. Tacrolimus was added to the regimen. A couple months later, the patient had another flare and was placed on high-dose corticosteroid therapy, whereas AZA was also discontinued for unspecified reasons. Although aminotransferases improved, they did not normalize again. A repeat biopsy at that time revealed grade IV inflammation with evidence of bridging fibrosis, despite adequate tacrolimus levels. At that point, the patient was started on sirolimus 2 mg daily. MMF and tacrolimus were discontinued. Sirolimus was titrated to 4 mg, and because of an AIH exacerbation, the patient was started on rituximab infusions. Five years after initiation of sirolimus, the patient had received 5 rituximab infusions. No further exacerbations were noted. Rituximab 375-mg/m^2 infusions were administered twice 6 months apart and then another 3 times yearly. The patient did not report any adverse events on these medications.

This regimen along with 5- to 10-mg daily prednisone therapy achieved sustained remission of the disease. The patient did not experience any significant adverse reactions other than headaches associated with tacrolimus.

Table 1 offers information on liver biochemistry, IgG levels, and sirolimus dose projected in time since sirolimus initiation. Figure 1 provides schematically the treatments and the timing of exacerbations before sirolimus initiation.

DISCUSSION

Treatment with prednisone or budesonide and AZA is the standard practice in AIH treatment.[2] A recent article by International AIH Group redefined AIH response criteria: complete response, insufficient response, nonresponse, remission, and intolerance to treatment.[4] The combination of corticosteroids with AZA can normalize liver biochemistry in 75%–80% of cases.[5] However, up to 13% incomplete remission, and up to 9% treatment failure have been reported.[6]

MMF and tacrolimus are second-line regimens. Tacrolimus induces biochemical remission in 68.9% of refractory AIH. MMF is most effective in cases of intolerance to first-line therapy, with biochemical remission of 73.5% and overall response rate up to 82%. However, the response rate in nonresponders to initial therapy was just 32%.[6,7] Tacrolimus may result in neurotoxicity, gastrointestinal disturbances, diabetes mellitus, nephrotoxicity, pruritus, and alopecia. MMF is generally safe; however, leukopenia, neutropenia, sepsis, gastrointestinal symptoms, headaches, hair loss, and paresthesias have been reported. MMF is absolutely contraindicated in pregnant patients.[6,7]

Rituximab has also been used for refractory AIH. It acts by depleting B cells, which facilitate T-cell response against autoantigens.[8–10] An analysis of patients with difficult to treat AIH receiving 2 doses of rituximab 1,000 mg reported improved biochemistry up until 24 months after rituximab therapy and lower corticosteroid needs. Five of 22 patients had AIH exacerbation.[11] Another study of patients who failed initial therapy and received rituximab described improvement of liver biochemistry by week 12. That study revealed one patient with AIH flare after rituximab.[8]

There is no significant experience in the treatment of AIH with sirolimus.[3] Sirolimus acts by inhibiting mammalian target of rapamycin (mTOR), a vital protein for the survival and function of immune cells.[3,12] In a case series, with 5 patients with refractory AIH, sirolimus achieved response in liver biochemistry.[3] Sirolimus side effects include stomatitis, dyslipidemia, edema, respiratory infections, and cytopenias.[13–15] The current case reports a patient with significant improvement in the liver biochemistry after sirolimus and rituximab

A

Dates	Prednisone (total daily dose in mg)	AZA (total daily dose in mg)	MMF (total daily dose in mg)	Tacro (total daily dose in mg)
Feb-15	60	75	0	0
Apr-15	5	75	0	0
Aug-15	5	75	0	0
Sep-15	40	75	0	0
Oct-15	5	75	0	0
Jan-16	5	75	0	0
Feb-16	60	100	1000	0
Mar-16	5	100	1000	0
Sep-16	5	100	1000	0
Oct-16	60	100	2000	0
Nov-16	5	100	2000	0
Sep-17	5	100	2000	0
Oct-17	60	150	3000	0
Nov-17	20	150	3000	2
Dec-18	20	150	3000	2
Jan-18	80	150	3000	2
Feb-18	10	0	3000	2
Oct-18	10	0	3000	2
Nov-18	10	0	0	0

B

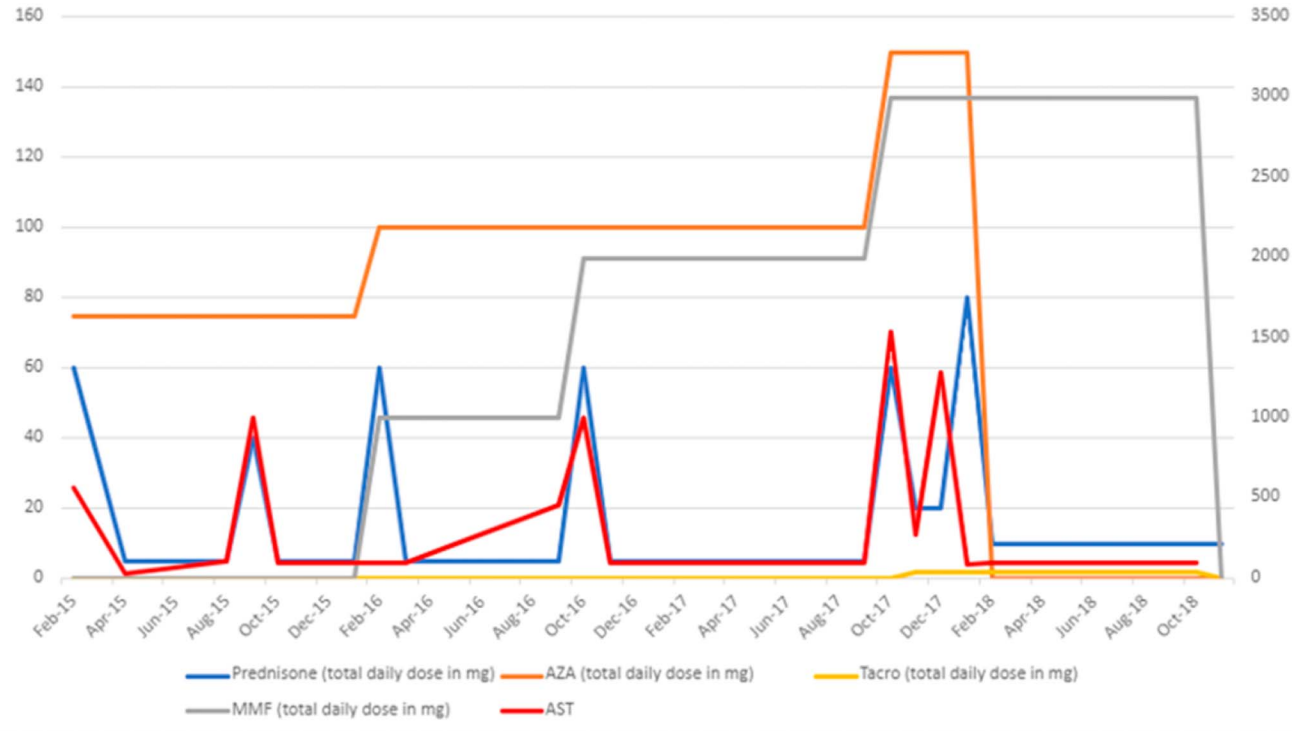

Figure 1. (A) Medications and doses used before sirolimus introduction in the treatment regimen. (B) Diagram depicting the medication trends and AST levels over time. Left y axis: Daily dose of prednisone, azathioprine, and tacrolimus in milligrams. Right y axis: Daily dose of mycophenolate mofetil in milligrams or AST levels in IU/L. *Represent the exacerbation episodes. AST, aspartate aminotransferase; AZA, azathioprine; MMF, mercaptopurine and mycophenolate mofetil.

therapy. It is challenging to attribute the clinical improvement on sirolimus alone, but an 18-month remission free period after the last rituximab infusion makes a case for sirolimus significant role in controlling AIH. For this patient, we provide trough and random sirolimus levels. Random levels varied between 14 and 19 ng/dL and trough levels were measured at 2–4 ng/dL. Previous studies reported median sirolimus blood level of 12.5 ng/dL in patients achieving a response. However, it was unclear whether this was a trough level.[3] It is evident that there is lack of information and only limited reports on sirolimus

role for AIH treatment. More studies are needed to understand appropriate management with sirolimus and combination with rituximab. Moreover, future studies should focus on identifying the correct dosage for initiation, maintenance of therapy, and target trough levels to keep the disease under control.

DISCLOSURES

Author contributions: S. Zouridis drafted the manuscript and created the tables/digital artwork; Y. Oo and W. Syn conceptualized the work added content to the manuscript; all authors revised the manuscript and gave final approval for publication. W. Syn is the article guarantor.

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