BRIEF OBSERVATION

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Use of Sirolimus in the Treatment of Refractory Autoimmune Hepatitis

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ABSTRACT

BACKGROUND: Corticosteroids and azathioprine are widely accepted as the initial therapy for autoimmune hepatitis. However, the disease is refractory to steroids in about 10%-20% of patients, for whom currently there is no standardized treatment. Here we describe our experience with sirolimus in treatment of steroid refractory autoimmune hepatitis.

METHODS: This is a longitudinal follow-up study. Between November 2007 and January 2014, 5 subjects with steroid refractory autoimmune hepatitis were treated with sirolimus at our institution.

RESULTS: A response, defined as a sustained >50% fall in alanine aminotransferase (ALT) levels, was achieved in 4/5 patients. A complete response, sustained normalization of ALT levels, was achieved in 2/5 patients. The need for steroids was significantly reduced in all patients ($P < .05$).

CONCLUSIONS: In this small series, sirolimus appears to be useful in the treatment of patients with steroid refractory autoimmune hepatitis.

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KEYWORDS: Autoimmune hepatitis; Sirolimus; Steroid-refractory

Autoimmune hepatitis is a chronic liver disease of unknown etiology.[1,2] The only widely recognized therapy for autoimmune hepatitis is glucocorticoids, frequently in combination with azathioprine. However, no response or an inadequate response occurs in 10% to 20% of patients, and drug side effects are seen in about 5% to 10% of patients.[1]

There is currently no standard treatment for patients in whom autoimmune hepatitis fails to respond to steroids. In patients intolerant of azathioprine, use of mycophenolate mofetil is recommended.[3] For those patients who are resistant to treatment with steroids and azathioprine, other immunosuppressive agents including calcineurin inhibitors (cyclosporine, tacrolimus) and mycophenolate have been used with variable success.[4] Another immunosuppressive drug, sirolimus, acts by inhibiting the mammalian target of rapamycin (mTOR), a protein that modulates the proliferation and survival of activated lymphocytes. mTOR inhibitors have largely been used in the prevention of rejection following solid organ transplantation and, more recently, for certain malignancies.[5] We describe the efficacy of sirolimus in the treatment of 5 consecutive patients with autoimmune hepatitis that was refractory to treatment with prednisone, azathioprine, and mycophenolate mofetil. The results of this report suggest that sirolimus may be useful in the treatment of this group of patients.

MATERIALS AND METHODS

A total of 5 subjects with a histological and serologically confirmed diagnosis of autoimmune hepatitis were studied. Each subject had a liver biopsy consistent with the diagnosis and had one or more autoantibodies known to be associated with autoimmune hepatitis. All of the patients had failed to respond, based on serum transaminase levels, to a combination of prednisone and azathioprine. Three of the patients also had received mycophenolate mofetil without benefit. At initiation of treatment with sirolimus, the dose of current

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immunosuppression drugs was left unchanged. We defined a response as at least a 50% fall in baseline alanine aminotransferase (ALT) levels that were sustained. A complete response was defined as a sustained normalization of ALT levels during treatment with sirolimus. Demographic and laboratory data including total bilirubin, aspartate aminotransferase (AST), ALT, alkaline phosphatase, white blood count, serum creatinine, serum triglyceride levels, and cholesterol levels were obtained before starting therapy and at frequent intervals thereafter. All sirolimus serum levels were obtained before the next morning's dose. Sirolimus was initiated at 2 mg/d in all patients. The dose of sirolimus was increased until serum levels of 10-20 ng/dL were achieved. Adverse events after the addition of sirolimus were noted.

CLINICAL SIGNIFICANCE

- Autoimmune hepatitis is refractory in 10%-20% of patients, and there is little consensus on how to manage these patients.
- Sirolimus appears to be useful in the treatment of patients with steroid refractory autoimmune hepatitis with acceptable side effects.
- Sirolimus may be a suitable alternative to more toxic drugs such as tacrolimus in the treatment of this difficult disease.

Statistical Analysis

Variables were tabulated with Microsoft Excel database (Microsoft Corporation, Redmond, WA) and results are presented as mean value ± SEM. Student's one-tailed *t* test was used for statistical analysis. A P value $< .05$ was considered significant. Certain results were reported as median with range due to small sample size and extremes of variables.

RESULTS

This is a longitudinal follow-up study. Between November 2007 and January 2014, 5 autoimmune hepatitis patients (3 male, 2 female) having persistent elevation of AST/ALT despite being on adequate dosage of steroids and other immunosuppressants, were treated with sirolimus. Demographic and medication data of the patients are presented in Table 1. Median patient age was 27 years (range 21-56 years). All patients were on steroids for at least 6 months before initiation of sirolimus (median 24 months, range: 6 months-8 years). All 5 patients had received azathioprine for at least 6 months as well (median 24 months, range: 6-36 months). Three of the 5 patients (patients 1, 3, and 4) were treated with mycophenolate in addition to steroids for a period of 2, 60, and 24 months, respectively. All 3 had required withdrawal of azathioprine due to the development of acute pancreatitis. Median serum sirolimus level during treatment was 12.5 ng/dL (range 10-30 ng/dL). The median treatment duration with sirolimus was 8 months (range 4-72 months). All 5 patients remain on sirolimus at the time of this report.

Laboratory data for patients at baseline and at the end of 3 months is shown in Table 2. Figure 1 illustrates various agents used and course after diagnosis of autoimmune hepatitis in Patient 1. Change in ALT levels in all study patients after introduction of sirolimus is shown in Figure 2. There was a significant improvement in the serum levels of AST, ALT, and total bilirubin. The need for steroids after 3 months of therapy was significantly reduced ($P < .05$). A response was achieved in 4/5 patients. A complete response was achieved in 2/5 patients.

Adverse Effects

Two of 5 patients had increased cholesterol and triglyceride levels after 6 months of treatment with sirolimus. One of them, however, had high baseline levels of total cholesterol and triglyceride level to begin with, and posttreatment levels were not significantly different. One patient had an episode of interstitial pneumonitis, which resolved and was not thought to be due to the sirolimus.

DISCUSSION

Standard treatment for autoimmune hepatitis includes prednisone, commonly with azathioprine. Approximately 80% of patients respond to this therapy with normalization of liver tests.[1] When patients fail to respond, there is little consensus on what immunosuppressive agents should be used.[6] None of the empiric salvage therapies has been incorporated into a standard management algorithm.

Table 1 Demographic and Medication Data of Study Patients

Patient	Age, Years	Sex	Duration Conventional Therapy	Prednisone Months	Aza	MMF	Sirolimus
1	21	M	6	6	6	2	24
2	27	M	24	24	24	0	6
3	25	M	96	96	36	60	8
4	39	F	36	36	12	24	72
5	56	F	24	24	24	0	4

Aza = azathioprine; MMF = mycophenolate mofetil.