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Case Report

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The Course of Liver Injury in Patients with Concomitant Chronic Hepatitis C Infection and Autoimmune Hepatitis after Treatment with Direct Acting Antiviral Agents: A Case Series

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Abstract

Autoimmune disease can co-occur in patients with chronic hepatitis C (HCV). Prior to direct acting antiviral agents (DAAs), HCV treatment was interferon, which causes non-specific immune activation and is contraindicated in patients with concomitant autoimmune hepatitis (AIH). Records of 5 patients with chronic HCV and biopsy-proven AIH who were treated with DAAs were evaluated. All patients achieved sustained virologic response and normalized ALT after DAA initiation. One patient was weaned off immunosuppression completely while two were weaned off budesonide and maintained on azathioprine after DAA therapy. One patient never required immunosuppression. Another had a recurrent flare of AIH post-DAA therapy while off immunosuppression, though is now controlled on azathioprine. This case series suggests treating patients with HCV and concomitant AIH with DAAs may promote short-term biochemical remission of AIH, though further studies are required to confirm these findings and evaluate for potential long-term benefit of DAA therapy in this population.

Keywords: Autoimmune hepatitis; Direct acting antiviral agents; Hepatitis C virus

Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus of the Flaviviridae family that results in chronic hepatitis in approximately 75-85% of infected individuals [1]. Previous studies have demonstrated a co-occurrence of various autoimmune diseases in patients with chronic HCV infection, including autoimmune thyroiditis, mixed cryoglobulinemia, and porphyria cutanea tarda [2,3]. A 2015 study of 77 patients discovered that 19% of patients with chronic HCV infection had ANA positivity alongside other associated autoantibodies [4]. In most of these cases autoantibody titers were low and the patients were histologically unchanged from those with HCV without autoantibodies. It is believed that in rare cases of genetically predisposed hosts, HCV infection can trigger autoimmune hepatitis (AIH) [5]. These patients have what is described as an autoimmune overlap syndrome as liver biopsies have features of chronic HCV as well as plasma cell infiltration characteristic of AIH [6].

Until recently the only available treatment for chronic HCV infection was interferon (IFN), an antiviral agent that nonspecifically up-regulates the cellular immune response. This activation of the immune system had made HCV treatment with IFN relatively contraindicated in patients with autoimmune hepatitis (AIH) [7]. It has also been understood that immunosuppressive therapy for AIH increases viral replication in chronic HCV, thus making disease control difficult to achieve [8]. With the advent of direct anti-

viral acting agents (DAAs) for chronic HCV infection, patients with concomitant AIH are now able to receive treatment [9]. The literature has yet to evaluate the disease course of AIH in patients with chronic HCV infection who have been successfully treated with DAAs.

We describe five cases of patients treated at a single urban, outpatient academic liver center with chronic HCV who developed biopsy proven AIH and demonstrated biochemical response to treatment with DAA therapy.

Methods

We performed a retrospective chart review of patients who were assessed at an academic outpatient transplant liver center with a laboratory confirmed diagnosis of HCV and biopsy-proven diagnosis of AIH. Patients' electronic medical records were assessed for demographic information, liver enzymes, HCV genotype, HCV viral load, autoantibody levels, and liver biopsy pathology results. Patients were followed from time of established care to June 2016. The study was approved by the Montefiore Institutional Review Board.

Results

Five female patients with chronic HCV infection (genotype 1 n=3, genotype 2 n=2) were diagnosed with AIH based on positive serology (anti-nuclear antibody n=5, anti-smooth muscle antibody n=1, anti-liver-kidney microsomal antibody n=1), elevated immunoglobulin G (mean =3,306mg/dL) and liver biopsy (Table 1). Two patients had previous treatment failure with IFN-based therapy. SVR was achieved in all patients (sofosbuvir + ribavirin n=2, simeprevir + sofosbuvir n=2, ledipasvir + sofosbuvir n=1). The average peak ALT prior to DAAs was 415U/L (range 135-1032U/L). All patients had complete normalization of ALT after initiation of DAAs (mean=3 months, range=2 weeks-13 months) (Figure 1). Two patients were weaned off AZA and budesonide with normal liver enzymes (mean ALT =12) more than 3 months after completing DAA therapy. Two patients underwent post-SVR liver biopsies for abnormal serum transaminases which showed evidence of active AIH. One of these patients had developed an acute flare following discontinuation of AZA with ALT 416U/L. Both patients remain on AZA more than 12 months after completing DAA therapy for maintenance therapy with biochemical remission. One patient never required immunosuppressive therapy.

	Case 1	Case 2	Case 3	Case 4	Case 5
DEMOGRAPHICS					
Age at time HCV Treatment	53	64	71	50	63
Sex	Female	Female	Female	Female	Female
HCV genotype	2	2	1	1	1
HCV peak VL	128127	2987686	9590033	3263873	10191663
Prior HCV treatment	None	None	Boceprevir, interferon, ribavirin	None	Interferon, ribavirin
HCV DAA used	Sofosbuvir, ribavirin	Sofosbuvir, ribavirin	Sofosbuvir, ledipasvir	Sofosbuvir, simeprevir	Sofosbuvir, simeprevir
Earlier Diagnosis (AIH or HCV)	HCV	HCV	HCV	HCV	HCV
AIH Treatment	Azathioprine, Budesonide	Azathioprine, Budesonide	None	Budesonide	Azathioprine
LABORATORY DATA					
Peak AST (U/L) before DAA	132	796	201	302	242
Peak ALT (U/L) before DAA	135	1032	239	310	357
ANA, homogenous pattern titer	1:160	1:160	1:320	1:40	1:640
IgG (mg/dL)	3010	4000	2295	1800	NA
Anti-smooth muscle Ab	Negative	Positive, 4+	Negative	Negative	Negative

LKM-Ab	Negative	N/A	N/A	Positive	Negative
Anti-DNA Ab	Positive	N/A	N/A	N/A	Negative
RF (IU/mL)	N/A	N/A	N/A	N/A	161
AMA	Negative	N/A	N/A	Negative	Negative
HISTOLOGY					
Prior liver biopsy findings	N/A	Moderately active HCV, mild-moderate interface hepatitis, stage 2/6 fibrosis	Mildly active HCV, stage 3/6 fibrosis	Minimally active HCV, stage 1/6 fibrosis	N/A
Liver biopsy findings at diagnosis of AIH	Moderately active, stage 1/6.	Moderately to severely active, stage 2/6.	Mildly to moderately active, stage 3-4/6.	Moderately active, stage 3/6 with moderate small droplet and large droplet steatosis.	Moderately active, stage 3/6, with mild small droplet steatosis.
Interface Hepatitis	2/4	3/4 – 4/4	2/4	1/4	2/4
Confluent Necrosis	0/6	0/6	0/6	0/6	0/6
Focal, lytic necrosis	4/4	3/4	2/4	1/4	2/4 – 3/4
Portal Inflammation	3/4	4/4	2/4	2/4	2/4
Fibrosis Stage	1/6	2/6	3-4/6	3/6	3/6
Repeat biopsy following DAA treatment	N/A	Mild-moderately active AIH	N/A	Mildly active AIH	N/A

Table 1: Patient Characteristics.

Discussion

This case series demonstrates that DAA therapy can achieve SVR in patients with chronic HCV infection and concomitant biopsy-proven AIH. Furthermore, treating this unique patient population with DAAs can promote biochemical remission of AIH. In this study, all patients had normalization of liver enzymes when followed after DAA therapy. One patient never required immunosuppressive therapy, and another has been successfully maintained off of AIH treatment over the last year. Two patients remain on AZA monotherapy. Only one patient had a recurrent flare of AIH post-DAA therapy after she stopped all immunosuppressive therapy for AIH and is currently controlled on AZA monotherapy.

Since the discovery of its causative agent in 1989, HCV has been linked to a multitude of immunopathological disease processes, including cryoglobulinemia, autoantibody production, B cell lymphoma, and autoimmune rheumatologic disease [10-12]. There have been multiple mechanisms proposed for the relationship between HCV and autoimmunity, though the overall pathophysiology remains poorly understood. HCV is a hepato- and lymphotrophic agent with an envelope protein E2 that binds to the human CD81 receptor [13]. This engagement of HCV lowers the B cell threshold for polyclonal activation, thus leading to the production of autoantibodies and cryoglobulins [14]. A significantly higher prevalence of HCV antibody and HCV RNA has been found in patients with essential mixed cryoglobulinemia associated with glomerulonephritis when compared with patients with noncryoglobulinemic glomerulopathies [15]. A different mechanism involving intracellular B lymphocyte infection by HCV appears to play a role in HCV-associated gammopathy and non-Hodgkin B-cell lymphoma [10]. Experiments have also revealed the pathogenic role of molecular mimicry with a cross-reactivity between CYP2E1 and specific sequences in the HCV-NS5b protein that promote the development of auto-antibodies, leading to more severe necroinflammation [16].

While the pathogenesis of AIH is incompletely understood, there is increasing evidence that genetic susceptibility, molecular mimicry, and impaired immunoregulation contribute to initiation and sustained autoimmunity [17-19]. Numerical and functional

defects of CD4(+) and CD25(+) regulatory T-cells are thought to play a permissive role in enabling autoimmune liver disease [18,19]. Patients with AIH have also been found to have significantly increased pro-inflammatory cytokines, such as IL-17F, IL-21, IL-23, IL-10, IL-6, and TNF [20]. Many viral etiologies have been associated with AIH, including measles, rubella, varicella-zoster, Epstein-Barr, and hepatitis B, C, D, and E [5,21-24]. It is hypothesized that cross-reaction between viral particles and liver auto-antigens serves as a trigger mechanism for virus induced AIH. Therefore, it is not surprising that there have been several reports in the literature about the co-occurrence of HCV and AIH, possibly due to virus-induced autoimmunity [5,25].

Many immune-based extra-hepatic manifestations of HCV have been found to improve with anti-viral treatment. Studies have demonstrated a significant drop in mixed cryoglobulin levels in those patients who achieved SVR, as well as improvement in arthralgias and myalgias [26,27]. There has also been found to be a lower cumulative incidence of lymphoma development in patients who eradicated HCV, suggesting that treatment may be preventative [28]. SVR was noted to induce NHL regression, while a viral relapse was followed by lymphoma recurrence [29,30]. AASLD guidelines had previously recommended different treatment prioritization for such patients to receive HCV treatment given the poor tolerance and low cure rate with IFN-based therapy. Now with the availability of DAAs and the continued literature demonstrating improvement of extra-hepatic manifestations of HCV with therapy, the current AASLD guidelines have eliminated such prioritization and recommend treating essentially all such patients [31].

Until recently, the standard of care for the treatment of HCV was IFN-based regimens, which are known to be poorly tolerated and especially problematic in patients with immune-mediated disease given their side effect profile and association with a wide variety of autoimmune toxicities [8]. IFN has also been associated with the development of frank autoimmune diseases such as systemic lupus erythematous, rheumatoid arthritis, sarcoidosis, and autoimmune thyroid disease. This phenomenon is thought to be mediated by widespread activation of the immune system, with B cells, T cells, and uninhibited action of antigen presenting dendritic cells implicated [32-34]. Furthermore, common side effects of IFN such as fever, fatigue, arthralgia, myalgia, and depression make drug side effect versus exacerbation of underlying disease nearly impossible to differentiate [34,35]. Alternatively, it has been understood that corticosteroid and immunosuppressant treatment for AIH increases viral replication in chronic HCV [36-38]. Magrin and colleagues noted a significant increase in viremia after three months of treatment with prednisone in fourteen patients with chronic HCV [37]. In a study by Calleja et al. eight patients with chronic HCV had a significant increase in ALT and bilirubin levels after receiving a four-month course of prednisone [38]. DAAs offer a treatment option to patients with autoimmune disease who were previously unable to take standard IFN-based therapies [8,39].

Conclusions

While this case series has demonstrated that patients with HCV and biopsy-proven AIH treated with DAAs can achieve SVR and often biochemical remission several months following HCV treatment, neither long-term biochemical response nor conditions in which to consider if and when to wean off immunosuppressive therapy have been assessed. Based on this limited data, we recommend continued close monitoring of liver enzymes following DAA therapy and judicious weaning of maintenance therapy for AIH after achieving at least several months of sustained biochemical remission. Further larger studies should be performed to evaluate the long-term biochemical response post-DAA therapy. Additionally, studies should assess the possible role of monitoring autoantibody levels pre- and post-DAA therapy to help predict which patients may be able to eventually successfully wean off immunosuppressive therapy for AIH.

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