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**Healing of autoimmune hepatitis associated with hepatitis C virus infection treated with direct-acting antivirals**

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**ABSTRACT**

The use of direct-acting antivirals (DAA) for the hepatitis C virus (HCV) has yielded a significant improvement in the treatment of autoimmune hepatitis (AIH) associated with HCV infection. Interferon was the cornerstone of HCV therapy before the introduction of these agents into the clinical practice. Herein, we report the case of an HCV-infected patient who developed an interferon-induced AIH and since then, has received immunosuppressive therapy. Administration of DAA resulted in a sustained virologic response (SVR) and clinical AIH remission which allowed a discontinuation of immunosuppressive treatment.

**Key words:** Hepatitis C. Autoimmune hepatitis. Interferon. Direct-acting antiviral.

**INTRODUCTION**

The association between hepatitis C virus (HCV) and autoimmune hepatitis (AIH) has been described in different clinical situations. Previously, there were few therapeutic

options for patients with chronic hepatitis C-AIH overlap syndrome as interferon-based antiviral therapies may enhance autoimmunity. Direct-acting antivirals (DAA) represent a promising treatment option for these patients (1).

## **CASE REPORT**

A 47-year-old, previously healthy female was referred to our unit for the first time for evaluation. She had a history of asthenia as well as elevated aspartate and alanine aminotransferase levels according to the blood tests (AST: 101 UI/l and ALT: 193 UI/l). A complete diagnostic workup was performed, which indicated an HCV infection with no other pathological findings. The metabolic study including iron balance, alpha-1-antitrypsin and ceruloplasmin and the autoimmunity study of antinuclear, anti-mitochondrial and anti-liver/kidney/microsome antibodies (ANA, AMA, and anti-LKM) and the hepatitis B serology were all negative. A liver biopsy revealed chronically active hepatitis. Chronic HCV was diagnosed and treatment with interferon alpha 2b three times per week was started. Three months later, an increase of the aminotransferases was detected (aspartate aminotransferase [AST]: 287 UI/l, alanine aminotransferase [ALT]: 365 UI/l). The immunological tests showed high AMA (1: 80) and anti-LKM (1:1,260) titers. A diagnosis of AIH 2b, probably due to interferon therapy, was established. Interferon therapy was stopped and immunosuppressive treatment with prednisone and azathioprine was started with the normalization of aminotransferases and immunity parameters. Maintenance treatment was modified in 2008 to azathioprine at 50 mg and budesonide at 6 mg per day. There were many unsuccessful attempts throughout the subsequent years to reduce the immunosuppressive medication, which were always accompanied by a worsening of liver function tests.

In September 2015, treatment with DAA was considered. A complete workup was performed, including a transient elastography that showed a liver stiffness of 5.2 Kpa (not significant fibrosis; F0-F1) and an abdominal ultrasonography that did not show signs of advanced hepatopathy. HCV genotype 1b and also a viral load of 1,815,585 UI/ml (6.26 log) was confirmed.

In January 2016, the patient started treatment with ledipasvir/sofosbuvir (Harvoni®) for a 12-week period and achieved an undetectable viral load without adverse effects. A liver biopsy was performed a year after finishing the treatment in order to consider the discontinuation of immunosuppressive treatment. There were no microinflammatory findings (Fig. 1), therefore, immunosuppressive therapy was discontinued. Since then, the patient has been asymptomatic with normal liver blood tests (Table 1).

## **DISCUSSION**

AIH is a hepatic disease with an unknown origin. It is characterized by the presence of chronic inflammation, necrosis and the presence of autoantibodies in blood tests. A favorable response to immunosuppressive treatment can be achieved in almost 70% of these patients (1).

The association between HCV and AIH has been reported in three clinical situations. First, patients infected with HCV have a higher prevalence of positive non-organ-specific autoantibodies than with other types of viral hepatitis. The ANA, AMA and anti-LKM antibodies can be harmful and cause hepatic damage, especially anti-LKM (2-4). On the other hand, HCV can enhance autoimmunity and perpetuate this activity, even when the virus has been eradicated. There are also some cases with chronic HCV accompanied by AIH, also known as chronic hepatitis C-AIH overlap syndrome (5). All of these situations represent a diagnostic dilemma, considering that AIH does not have specific criteria. It also represents a therapeutic problem. On the one hand, corticosteroids as the standard treatment of the AIH may enhance HCV replication and, on the other hand, interferon treatment has been reported to activate the immune system, leading to an exacerbation of AIH (6-9).

We report the case of a patient with a chronic HVC infection who suffered AIH that was related to interferon therapy. A sustained virological response was achieved with DAA and once HCV was eradicated, immunosuppressive treatment was successfully discontinued. This fact might confirm the pathogenic role of HCV infection for the maintenance of hepatic autoimmunity in this patient.

Information with regard to the treatment of chronic HCV-AIH syndrome with DAA is limited. As far as we know, only one case report has been described in the medical literature that involved one patient with a diagnosis of overlap syndrome, who was treated with DAA. The case was a 50-year-old male with an HVC infection, high titer of ANA autoantibodies and AIH confirmed by liver biopsy (10). He was treated with daclatasvir/asunaprevir and obtained a sustained virological response with no adverse effects. He was finally able to discontinue immunosuppressive treatment.

In our clinical experience, DAA can be a safe and effective treatment for overlap syndrome, at least in some patients. Further studies are required to confirm if the eradication of HVC could be a way to discontinue immunosuppressive therapy in selected patients.

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**Table 1. Blood tests\***

	1996 (when AIH was diagnosed)	2016 (before DAA introduction)	2016 (after four weeks of treatment)	2018 (a year after discontinuing immunosuppressive therapy)
<i>Aspartate aminotransferase (AST)</i>	101 U/l	99 U/l	13 U/l	11 U/l
<i>Alanine aminotransferase (ALT)</i>	193 U/l	160 U/l	12 U/l	12 U/l
<i>Gamma-glutamyl transferase (GGT)</i>	26 U/l	30 U/l	12 U/l	11 U/l
<i>Alkaline phosphatase (ALP)</i>	90 U/l	89 U/l	58 U/l	99 U/l
<i>Bilirubin</i>	0.5 mg/dl	0.7 mg/dl	0.3 mg/dl	0.6 mg/dl
<i>Prothrombin time and international normalized ratio</i>	No pathological findings	No pathological findings	No pathological findings	No pathological findings

\*Blood tests were performed since the diagnosis of AIH until the present time, after discontinuing immunosuppressive treatment.



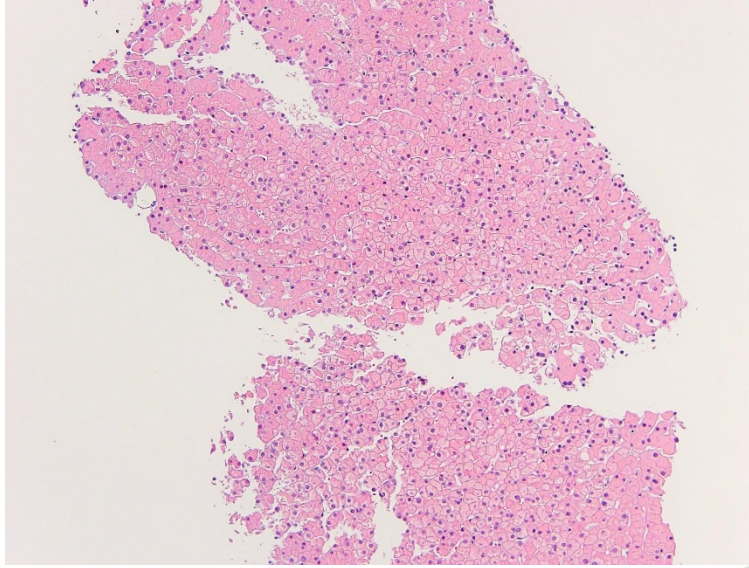


Fig. 1. Percutaneous hepatic biopsy with five fragments between 0.1-0.3 cm by 0.7 cm in length. There were no signs of lobular hepatitis on examination with hematoxylin and eosin x100.