RESEARCH LETTER

Risk of autoimmune hepatitis reactivation in patients with chronic hepatitis C and autoimmune hepatitis treated with direct-‑acting antivirals

Katarzyna Fleischer-Stępniewska[1], Weronika Rymer[1], Marcin S. Inglot[2], Małgorzata Zalewska[1], Brygida Knysz[1], Małgorzata Inglot[1]

1 Department of Infectious Diseases, Liver Diseases and Acquired Immune Deficiences, Wroclaw Medical University, Wrocław, Poland
2 Department of General and Pediatric Radiology, Wroclaw Medical University, Wrocław, Poland

Introduction   The prevalence of autoimmune hepatitis (AIH) is 160 to 170 per 1 000 000 population in Europe, with women being more frequently affected.[1] According to the International Autoimmune Hepatitis Group (IAIHG) scoring system last revised in 2015, AIH is diagnosed on the basis of biochemical and serological tests along with histologic examination of the liver.[1,2] Optimal therapy is challenging when AIH is accompanied by chronic hepatitis C, as these 2 conditions require different therapeutic strategies. Until 2014, the only available antiviral therapy was interferon alfa, associated with the risk of exacerbation of autoimmune diseases. On the other hand, immunosuppressive treatment could enhance viral replication. The new interferon-free regimens with direct-acting antiviral agents (DAAs) are promising for this difficult-to-treat population.[3] In 2015, an estimated 71 million people suffered from chronic hepatitis C virus (HCV) infection, with the highest reported prevalence in the Eastern Mediterranean Region and European Region according to the World Health Organization.[4] The prevalence of HCV infection with concomitant AIH remains unknown. New effective therapies are now broadly available; however, data regarding the safety and efficacy of DAAs in these patients are limited.

The aim of this study was to evaluate the potential impact of interferon-free antiviral therapy on AIH activity in patients with HCV infection and AIH in a long-term follow-up.

Patients and methods   This prospective single-‑center observational study was conducted between January 2015 and March 2018. Patients were recruited from a named patient program created to ensure early access to interferon-free therapy for patients with the risk of unfavorable course of chronic HCV infection. Antiviral medications were provided by the manufacturer (AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany). Adult patients with chronic HCV genotype 1b infection with definitive or probable AIH were enrolled. Patients with HIV or hepatitis B virus coinfection, other concomitant liver diseases, and hepatocellular carcinoma were excluded. Screening for hepatocellular carcinoma included serum α-fetoprotein measurement and abdominal ultrasound within 1 month prior to antiviral therapy. Patients declared no drug or alcohol abuse as well as no hepatotoxic drug use for at least 6 months prior to the study. Patients following previous antiviral treatment other than DAA and immunosuppressive therapy were eligible, provided there were no contraindications to antiviral therapy.

Four patients met the protocol criteria. All patients were white Europeans. The clinical characteristics of the patients are presented in **TABLE 1**.

Antiviral treatment with ombitasvir/paritaprevir (boosted with ritonavir) and dasabuvir (3D), with or without ribavirin (OBV/PTV/r/DSV ±RBV; 3D ±RBV) was scheduled for 12 weeks. The dose of coformulated OBV/PTV/r was 25 mg/d, 150 mg/d, and 100 mg/d, respectively, and the dose of DSV was 500 mg/d divided into 2 doses. One patient received RBV at a dose of 1200 mg/d.

There were 7 time points with laboratory testing and clinical assessment: baseline, 1st week of therapy, 4th week of therapy, end of treatment, as well as 24-week, 48-week, and 2-year follow-up.

TABLE 1 Characteristics of patients, a course of antiviral therapy, and follow-up results

No.	Sex / Age, y	Coincidence of AIH and HCV, AIH therapy	Immune disorders associated with AIH	IAIHG scoring at baseline, points	HCV genotype/ baseline HCV RNA, IU/ml	Interferon-free therapy schedule[a]	Liver fibrosis, kPa/METAVIR score Baseline	At 24 weeks and 2 years	Adverse events during therapy and at follow-up
1	M/34	Idiopathic AIH-1 confirmed by liver histology at the age of 14; in remission since 2005; acute hepatitis C at the age of 25; HCV-treatment naive; cirrhotic at baseline. **Summary**: AIH with acquired HCV; no AIH treatment at baseline	Ulcerative colitis	18, definite AIH	1b 46 400	12 weeks; 3D+RBV	21.42/F4	18.62/F4 17.14/F4	Biochemical and clinical manifestation of hepatitis with exacerbation of ulcerative colitis at 9 weeks of follow-up
2	F/37	Idiopathic AIH-1 confirmed by liver histology at the age of 9; budesonide (switched from prednisone due to typical side effects) with azathioprine since 2012, with AIH remission; HCV diagnosed at the age of 20; HCV treatment-naive. **Summary**: AIH with acquired HCV; immunosuppressive therapy at baseline (budesonide, 3 mg/d, with azathioprine, 50 mg/d)	None	16, definite AIH	1b 981 000	12 weeks; 3D	14.04/ F3–4	8.6/F2 7.38/F2	Exogenous Cushing syndrome at 2 weeks of therapy
3	F/54	Acute hepatitis C at the age of 37 (probable); noncirrhotic; treatment-experienced: 1) recombinant interferon alfa 2b/RBV (1999) with viral relapse and interferon-induced thyroiditis; and 2) pegylated interferon alfa 2a/RBV (2003) with viral relapse; AIH-1 confirmed in 2011 by liver histology, with arthritis. Budesonide (switched from prednisone due to typical side effects) and azathioprine since 2011, with AIH remission. **Summary**: chronic hepatitis C with AIH (possibly interferon-induced); immunosuppressive therapy at baseline (budesonide, 3 mg every second day, with azathioprine, 25 mg/d)	Hashimoto thyroiditis (1999); polyarthralgia involving the small joints without arthritis (2011)	14, probable AIH	1b 10 400 000	12 weeks; 3D	11.12/F3	5.24/F2 5.28/F2	Exogenous Cushing syndrome at 2 weeks of therapy; withdrawal of immunosuppressive therapy at 48 weeks
4	F/70	Chronic hepatitis C diagnosed at the age of 51; treatment-experienced: recombinant interferon alfa 2b/RBV (1999) with viral relapse; arthritis and ASMA-positive hepatitis (2012); AIH-1 confirmed by liver histology (2014); no AIH treatment at baseline. **Summary**: chronic hepatitis C with AIH (possibly interferon-induced); no AIH treatment at baseline	Graves–Basedow disease (1982); polyarthralgia involving the small joints without arthritis (2012); mucosal dryness (2012)	16, definite AIH	1b 7 000 000	12 weeks; 3D	9.48/F2	5.8/F0 5.02/F0	No hepatitis flare; no AIH treatment

a   Schedule according to the manufacturer's instructions at the time of the study

Abbreviations: AIH, autoimmune hepatitis; ASMA, anti-smooth muscle antibodies; DAA, direct-acting antiviral agent; F, female; HCV, hepatitis C virus; IAIHG, International Autoimmune Hepatitis Group scoring system last revised in 2015; M, male; 3D, ombitasvir/paritaprevir (boosted with ritonavir) and dasabuvir; 3D+RBV, ombitasvir/paritaprevir (boosted with ritonavir) and dasabuvir with ribavirin

At every visit, patients underwent routine clinical assessment and basic laboratory testing. Liver function was assessed using the Child–Pugh and Model for End-Stage Liver Disease scores. Adverse events and laboratory abnormalities that occurred during treatment and at 24-week follow-up were evaluated according to common toxicity criteria (Common Terminology Criteria for Adverse Events version 4.0 by the National Cancer Institute of the National Institutes of Health). HCV RNA was measured by real-time polymerase chain reaction using the GeneProof Hepatitis C PCR Kit (GeneProof a.s., Brno, Czech Republic) and performed on a Rotor-Gene 3000 (Corbett Research, Australia; sensitivity (limit of detection), 7.87–208.544 IU/ml; linear range, 10^{10}–25 IU/ml ±0.5log). The immune activity of AIH was assessed at baseline, end of treatment, and at 24-week and 2-year follow-up, using serum protein electrophoresis test (Capillarys Protein(e) 6, CAPILLARYS 2, Sebia, France), the measurement of immunoglobulin M and G levels (COBAS 6000 Modular biochemistry analyzer, Roche, city, Germany), and the measurement of antinuclear, anti–smooth muscle, antimitochondrial, and liver-kidney microsomal type 1 antibodies (indirect immunofluorescence method; Mosaic Basic Profil 1, EUROIMMUNE, Lubeck, Germany; a fluorescence microscope with a ×40 objective), with the titer calculated based on the dilution factor.

Liver fibrosis was evaluated at baseline and at 24-week and 2-year follow-up, with real-time shear-wave elastography (SWE), using the Aixplorer US system (SuperSonic Imagine S.A., Aix-en-Provence, France) with a convex broadband probe (SC6-1). Liver stiffness was measured in 5 different circular regions of interest in the right lobe of the liver, through intercostal spaces performed by an experienced radiologist. Tissue elasticity was expressed in kilopascals (kPa), and the corresponding METAVIR score was calculated according to the cutoff values of SWE validated for hepatitis C.[5]

The study was conducted in accordance with the Declaration of Helsinki for Human Research, and the protocol was accepted by the local Bioethics Committees of the Medical Chamber (1/BO/2014). All patients provided written informed consent prior to inclusion in the study.

Results All patients achieved sustained viral response with negative HCV RNA at 2 years, and showed persistent decline in α-fetoprotein levels and liver stiffness (TABLE 1).

Patient No. 1 presented with ulcerative colitis exacerbation and hepatitis flare with elevated liver enzyme activity (aminotransferases 5 times the upper limit of normal), increased immunoglobulin G levels, and the presence of anti–smooth muscle antibodies (previously negative) at 9 weeks of follow-up. Due to liver cirrhosis and low platelet count, liver biopsy was not performed because it is a high-risk procedure.

Prednisone monotherapy was introduced, followed by addition of azathioprine as AIH reactivation was suspected (12 points in the IAIHG scoring system). Biochemical recovery was achieved within 6 weeks. No liver decompensation or HCV infection reactivation was observed at 2 years.

Two patients (No. 2 and 3) treated with budesonide developed exogenous Cushing syndrome with moderate clinical manifestation in the first 2 weeks of 3D treatment despite a reduction in glucocorticoid dose according to the patient information leaflet. Symptoms subsided after further glucocorticoid dose reduction. Both patients continued with modified treatment, and patient No. 3 permanently stopped immunosuppressive therapy at 48 weeks, with no further hepatitis flare.

Patient No. 4 did not start immunosuppressive therapy, although its implementation was considered before antiviral treatment. The reason was normalization of AIH activity after HCV eradication.

We observed some fluctuations in autoimmune marker levels, with an inconclusive decrease of γ-globulins and immunoglobulin G levels in most patients and the appearance of previously absent antibodies. Additional data are provided in Supplementary material, *Table S1*.

Discussion The choice of optimal therapy strategy in chronic HCV infection and comorbid autoimmune liver disorders is challenging. New highly effective interferon-free regimens allow a rapid HCV elimination in this population of patients.[3,6] Apart from the previously reported good virological and biochemical response, we observed a decrease of liver stiffness on SWE. The impact of sustained viral response on liver stiffness was reported in patients treated with immunomodulating interferon-based regimens.[7] As there is no evidence for the direct anti-inflammatory effect of DAAs, our results suggest the absence of HCV replication as the cause of sustained fibrosis regression. However, it is important to note that necroinflammatory hepatic activity in AIH might also have influenced liver stiffness in SWE assessment.

Drug–drug interactions are one of the important negative aspects of DAA therapy. We observed moderate exogenous Cushing syndrome in the patient treated with budesonide. Such interactions were previously observed because CYP3A4 inhibitors may repeatedly increase the systemic availability of budesonide.[8] Contemporary next-generation DAAs allow the use of regimens without strong CYP3A4 inhibitors.

The most important clinical finding of our study is the impact of effective DAA therapy on the course of AIH. In one patient, immunosuppressive therapy was withdrawn after HCV elimination. On the other hand, one patient experienced the biochemical and clinical manifestation of hepatitis flare with an exacerbation of

ulcerative colitis. De novo AIH or exacerbations during or after antiviral therapy with interferon alfa were previously reported.[9] As there are no data on the immunomodulating activity of DAAs, we suggest that reactivation of AIH was associated with effective antiviral therapy. We hypothesized that elimination of HCV in situ resulted in immune recovery. The assumption was based on the experience with immune reconstitution inflammatory syndrome in HIV-infected patients.[10] The very short time between successful antiviral therapy and AIH reactivation may indicate such a relationship. Dikopoulos and Zizer[11] reported a possible AIH exacerbation a few weeks after DAA therapy, although this was not confirmed by liver histology.[11] We also considered a drug-induced autoimmune liver disease. Matsumoto et al[12] reported a case of DAA-associated drug-induced AIH during DAA therapy in an 81-year-old woman without previous autoimmune disorders. Our patient did not fulfill the criteria for drug-induced autoimmune liver disease. Although the histological assessment could be conclusive, liver biopsy was contraindicated in our patient.

This study has certain limitations, including the small group size and heterogeneity in terms of the etiology of AIH. Both limitations result from the epidemiology of concomitant HCV infection and AIH and a single-center study design. We present our results despite these limitations because the design of the study allowed us to observe a good response to interferon-free therapy and the risk of reactivation of AIH in these difficult-to-treat patients. These observations may have significant clinical implications.

In conclusion, patients with AIH and HCV infection can be effectively treated with DAAs with a positive effect on liver stiffness. Drug–drug interactions need to be evaluated before and during DAA treatment. Finally, patients with AIH and HCV infection treated with DAAs should be screened during and after the therapy for possible AIH flare and drug-induced liver injury.

SUPPLEMENTARY MATERIAL

Supplementary material is available with the article at www.mp.pl/paim.

ARTICLE INFORMATION

REFERENCES

1 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune Hepatitis. J Hepatol. 2015; 63: 971-1004.

2 Manns MP, Lohse AW, Vergani D. Autoimmune Hepatitis-Update 2015. Journal of Hepatology. 2015; 62: S100-S111.

3 European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. European Association for the Study of the Liver. J Hepatol. 2018; 69: 461-511.

4 Global hepatitis report 2017. World Health Organization website. http://www.who.int/iris/handle/10665/255016. Accessed January 4, 2019.

5 Ferraioli G, Tinelli C, Dal Bello B, et al. Liver Fibrosis Study Group. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012; 56: 2125-2133.

6 Sugiura A, Wada S, Mori H, et al. Successful treatment for chronic hepatitis C-autoimmune hepatitis overlap syndrome due to daclatasvir and asunaprevir. Case Rep Gastroenterol. 2017; 11: 305-311.

7 Mendoza J, Trapero-Marugán M, González-Moreno L, et al. Hepatic fibrosis in patients with chronic hepatitis C assessed by transient elastography: implications for determining the efficacy of antiviral therapy. Rev Esp Enferm Dig. 2010; 107: 426-434.

8 Pereira MT, Ferreira L, Horta AA, et al. Exogenous Cushing's syndrome as a result of ritonavir-budesonide interaction – a case report. HIV and AIDS Review. 2016; 15: 91-93.

9 Rigopoulou EI, Zachou K, Gatselis N, et al. autoimmune hepatitis in patients with chronic HBV and HCV infections: patterns of clinical characteristics, disease progression and outcome. Ann Hepatol. 2013; 13: 127-135.

10 Price P, Mathiot N, Krueger R, et al. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol. 2001; 22: 279-287.

11 Dikopoulos N, Zizer E. Coincidence of a chronic Hepatitis C and an autoimmune Hepatitis Type 3 - successful therapy with the new direct-acting antiviral agents. Z Gastroenterol. 2016; 54: 770-773.

12 Matsumoto K, Kikuchi K, Kajiyama Y, et al. Development of autoimmune hepatitis during direct-acting antiviral therapy for chronic hepatitis C virus infection: a case report. Intern Med. 2018; 57: 2669-2673.